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(22) Application Date:

30 January 2003

(21) Application No.:

P-200300025

(54) Title:

Preparation of new pharmaceutically usable formulations of losartan by new methods of purification and isolation

For issuing of said document the stamp at the amount of 255.00 SIT paid according to first paragraph, no. 4 of the stamp tax of the Law Act governing the stamps (The Official Gazette of RS, No. 8/00 and further).

Ljubljana, 19 January 2005

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Kotnikova 6, 1001 Ljubljana, POB 206, telephone: 01/478 3100, fax: 01/478 3111

REQUEST FOR A PATENT GRANT	
<b>1. Address for correspondence:</b>  LEK Pharmaceuticals d.d. Intellectual Property Department Verovškova 57, SI – 1526 Ljubljana, Slovenia  Telephone: 580 20 05 Fax: 568 2123      code: pš/131	<b>Acknowledgement of the application</b> <i>(for official use only)</i>  Date of application receipt:  30 January 2003  Application number: P-200300025
<b>2. Applicant</b> (Family name followed by given name and address; for a legal entity, full official designation) Lek Pharmaceuticals d.d. Verovškova 57 SI - 1526 Ljubljana Slovenia	<b>Stamp and signature:</b>
<b>3. Representative:</b>	<b>Registration No.:</b>
<b>4. Inventor</b> (Family name followed by given name and address):  Ljubo Antončič, Podmiljščakova 43, SI-1000 Ljubljana	
<b>5. Title of invention:</b>  Preparation of new pharmaceutically usable formulations of losartan by new methods of purification and isolation	
<b>6. Claimed priority right:</b>	
<b>7. Additional requests:</b> <input type="checkbox"/> application for a shortened duration patent <input type="checkbox"/> preliminary publication after the expiry of ____ months <input type="checkbox"/> application is divided from the application no.: ____	
<b>8. Statements:</b> <input type="checkbox"/> statement of common representative	

**9. Enclosures:**

- x Description of the invention, having 30 pages
- x Patent claim (claims), having 4 pages; number of claims: 26
- x Schemes (if required for patent description); number of sheets: 20
- x Abstract
- ☐ Voucher for the settlement of fees
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A. Košak

\_\_\_\_\_  
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Lek Pharmaceuticals d.d.

*Slovenian Intellectual Property Office  
Kotnikova 6, 1000 Ljubljana*

Verovškova 57  
SI - 1526 Ljubljana  
Slovenia

Phone: +386 1 580 21 11  
Fax: +386 1 568 35 17

**Intellectual Property  
Department**

Phone: +386 1 580 20 05  
Fax: +386 1 568 21 23

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Annex to Request for Patent Grant

Information about additional inventors:

Preparation of new pharmaceutically usable formulations of losartan by new methods of purification and isolation

Anton Čopar, Staretov trg 1 SI-1275 Šmartno pri Litiji

## **Preparation of new pharmaceutically usable formulations of losartan by new methods of purification and isolation**

### Field of the invention

(IPC<sup>7</sup> A 61 K, A 61 K 9/19)

The present invention belongs to the field of chemistry of heterocyclic compounds and pharmaceutical industry and relates to a new mode of the preparation of pharmaceutically useful crystalline and amorphous alkali and alkali-earth salts of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole known under the generic name losartan and to the new process of isolation and purification to obtain highly pure said salts.

### Technical problem

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole acts on the last step of the cascade renin-angiotensin system by binding to the angiotensin II receptor. By utilizing said biochemical effect losartan is generally used as an effective antihypertensive agent in the form of the potassium salt (referred to as losartan potassium).

There is a need for highly pure losartan and losartan potassium, respectively, and for a novel process for its preparation by which the desired substance would be obtained in a simply performable and rugged way and with a high yield and high purity. It is also desirable to have the active substance in such a form to be simply incorporated into a pharmaceutical formulation which affords high bioavailability. To be incorporated into a pharmaceutical formulation the active substances must have defined desired physicochemical properties.

### Prior art

The substituted imidazoles with the action on the renin-angiotensin system of the blood pressure regulation including losartan are disclosed in the patent EP 253310 and US Pat. No. 5,138,069.

The applicants of the patent EP 253310 have protected in general different substituted imidazoles and the salts thereof, including ammonium, calcium, potassium and sodium salts and, specifically have described the reactions leading to potassium and sodium salts of certain substituted imidazoles and have described the products thereof. Surprisingly, the compound 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole, later known as losartan, in the experimental part it was described only in a non-salt form, that is, in an amphoteric form. The experimental part of that patent discloses that in the synthesis of losartan from cyanobiphenyl intermediate (that is from 2-*n*-butyl-4-chloro-1-[(2'-cyanobiphenyl-4yl)-methyl]-5-(hydroxymethyl)imidazole) with sodium azide losartan is produced in the form of slightly yellow crystals. Said patent application also compares the efficacy of the sodium salt 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole in lowering blood pressure before and after furosemide administration to the animals, however, the compound in the patent or any other application is neither characterized nor entered in the register of Chemical Abstract.

Chemical Abstracts Register, among the compounds with losartan structural formula or salts thereof, describes losartan in its basic that is amphoteric form; compounds with tetrahydrofuran and with pyridine; a mixture with hydrochlorothiazide, acid addition complexes hydrochloride hydrobromide, and of the salts *p*-toluenesulfonate and a potassium salt, and hydrochloride of a potassium salt. This suggests that the other alkali and alkali-earth salts of losartan have not been characterized and thus their useful properties are unknown.

For incorporation into a pharmaceutical formulation, pharmaceutical active substances must have defined desired physicochemical properties such as: solubility in water and certain solvents, suitable particle size, stability, nonhygroscopicity; which can be regulated by selecting an appropriate salt, adduct, complex and form thus achieving effective bioavailability.

Alkali or alkali-earth salts of losartan may be prepared because of the acid hydrogen atom on the tetrazole ring which can be split with a sufficiently strong base, that is with such base which provides the pH of an aqueous solution at the equivalent point, which according to US Pat. No. 5310928 is about pH = 10. EP 324377 describes the process for the formation of a potassium salt of losartan with potassium hydroxide; thereafter a potassium salt has been adopted as the most convenient form of the molecule for pharmaceutical use.

A similar process for preparing crystalline losartan potassium is disclosed in the patent WO 02094816 where, unlike the said process, an aqueous solution of potassium hydroxide is not used but a solid potassium hydroxide is added to the alcoholic solution of losartan.

According to the process of the synthesis disclosed in US Pat. No. 5,130,439 and US Pat. No. 5,310,928, crystalline losartan potassium is formed *via* substituted boric salts with the hydrolysis of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole with sulfuric acid in tetrahydrofuran and subsequent rinsing on the column with dipotassium hydrogen phosphate and by concentrating the rinsed aqueous solution with added *i*-propanol. This patent also describes the process for the preparation of losartan potassium but it is not reported whether losartan potassium produced by spray drying is crystalline.

From the disclosure it is clear that potassium hydroxide and dipotassium hydrogen phosphate are commonly used as the base in conversion of losartan to losartan potassium. Generally, under nonaqueous conditions, salts of certain heterocyclic compounds may be prepared with alkali or alkali-earth alcoholates which is

already known with certain tetrazolic compounds according to EP 495626 but not with losartan itself.

It has been found that losartan potassium exists in two polymorphic forms [Pharm. Res. 10 (1993), 900]. The authors of US Pat. No. 5,608,075 present that polymorphic form I characterized by DSC endotherm at 229.5°C while heating transforms to polymorphic form II characterized by the endothermic peak of melting at 273.2°C.

From the disclosure of US Pat. No. 5,859,258 it is clear that polymorphic form itself does not provide the needed suitable physicochemical properties. It was has been found that uncontrolled crystallization may lead to formation of large three-dimensional complexes which are unsuitable for incorporation into a pharmaceutical formulation and, in the said patent, a strictly controlled process is disclosed wherein, surprisingly, 14 different requirements should be met to obtain a suitable form of the particles for pharmaceutical use. The need for such strictly controlled process due to non-ruggedness may result in a number of errors in large-scale production which may essentially influence the final product.

The authors of US Pat. No. 5,128,355 have prepared and characterized certain compounds which are structurally very similar to losartan. Surprisingly, bromo- and iodo-analogs of losartan: 2-*n*-butyl-4-bromo-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole and 2-*n*-buthyl-5-hydroxymethyl-4-iodo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole are amorphous substances, whereas 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole (losartan) is a crystalline substance. Surprisingly, the compound 2-*n*-propyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-imidazole, described in that invention, distinct from losartan only in one side chain, is amorphous.

Surprisingly, according to the prior art it was not possible to prepare an amorphous form of losartan potassium itself. Losartan was as a crystalline product in all

prepared formulations [Egypt. J. Pharm. Sci. 40, (1999), 49]. It is known that in certain examples when pure compounds cannot be obtained in an amorphous form, pharmaceutically acceptable ingredients are added to separate the active substance in a solid-state form without formation of a repetitive crystal lattice which is characteristic of an amorphous state. From WO 0142221 it is known that celecoxib, known in several polymorphic forms, was prepared as an amorphous form only with the addition of crystallization inhibitors such as polyvinylpyrrolidone or hydroxypropylmethylcellulose, the resulting composites had increased bioavailability due to amorphous nature of the compound. US Pat. No. 6,284,277 discloses pharmaceutical formulations prepared by lyophilization that are a combination of an amorphous and crystalline phase wherein predominantly amorphous active substances and mannitol were combined with predominantly crystalline alanine. Among many active substances listed in said patent there is also losartan, however it is neither presented in any example nor said whether it is a potassium salt.

Crystal forms are identified by the physicochemical methods to measure the parameters dependent on the molecular environment. The most useful methods are: differential thermal analysis, infrared spectroscopy, solid-state nuclear magnetic resonance and X-ray diffraction.

Infrared spectroscopy is a method which on the basis of absorption of the IR light detects low-energy transitions particularly at a level of the bonds resulting from molecular vibrations and oscillations. They predominantly depend on the nature of the molecules and its bonds, and may be also influenced by the molecule environment. Therefore, it has become a widely accepted method for characterization of polymorphs. It is not always necessary that different crystal forms are also expressed on different IR spectra. Distinctions may be manifested in the presence or absence of defined oscillations or vibrations, in strengthened or weakened bands and in shifts of the wavelengths in individual oscillations or vibrations. It also holds true for an amorphous substance that the IR spectrum is not necessarily distinct from a crystal form, usually it is about the absence of

certain bands which are the function of intermolecular bonds present being in orderly state in a crystal.

Solid-state  $^{13}\text{C}$  nuclear magnetic resonance is a useful method for structural elucidation of solid samples. This way, individual polymorphic modifications can be determined. In a simple way, solvates may be characterized, and conformational polymorphs may be also examined in a very simple way. The spectra with high resolutions and the signals with good intensities are obtained by the CP/MAS (cross-polarization / magic angle spinning spectrum) scanning technique. [Sedon K.R. et al, Crystal Engineering: The Design and Application of Functional Solids, Kluwer Academic Publishers, 1999]. It would be expected that two identical spectra are obtained when two different polymers are recorded since in both cases two carbons are bonded in the same way. In fact, a distinction is evident because equivalent compounds are in different chemical environments [Bugay D.E.: Magnetic Resonance Spectrometry in: Brittain H.G., Physical Characterization of Pharmaceutical Solids]. Characterization of the structure of the samples which are pure and comprise only one crystal structure is the most simple. If there is a mixture of different forms, chemical shifts are obtained which may mutually overlap thus being misleading in characterization of a crystal structure. This may lead to an erroneous conclusion there is a new polymorphic modification. The spectrum of an amorphous form is usually simpler because of the absence of certain formation which in crystal forms the function of the specific environment in which the nuclei are present, and in an amorphous form the said environment is nonrepetitive, and the peaks are usually widened in an amorphous form.

Essentially, the crystal lattice may be characterized more precisely by X-ray diffraction than by infrared spectroscopy and NMR methods for solid samples wherein the changes are detected only on those atoms and bonds which directly interfere with the neighbouring molecules. From the X-ray diffraction pattern of a good orderly state of a large crystal a spatial assignment pattern of the molecule can be precisely defined, and by recording powder samples, the distinctions between different crystal lattices may be characterized but the position of individual atoms cannot be exactly characterized. In addition to identification of a

different assignment of the molecules in a crystal, indicating a different crystal form, information about the orderly state level or crystallinity can be obtained from the powder diffractogram wherein less orderly state is exhibited in broadening of the bands in the diffractogram. Extremely disordered state of a solid substance is an amorphous state which does not exhibit a repetitive pattern of molecular orientation in a solid substance therefore resulting in a diffuse scattering of X-ray light which is expressed by continuous diffraction in the diffractogram over the entire scanned region. Using the described method, several different crystal forms in the substance can be revealed and their mass ratio characterized. X-ray powder diffraction is a key method useful in distinguishing different crystal forms and for distinguishing an amorphous form from a crystal form when no distinction is feasible the other methods, for example IR and  $^{13}\text{C}$  CP/MAS NMR spectroscopy.

X-ray diffraction, after the substance has been characterized by different analytical techniques, is a key method useful for distinguishing an amorphous form from a crystal form since the substance can be identified as amorphous on the basis of the absence of diffractions at all angles on its X-ray powder diffractogram.

It is known that because of administration into the body, pharmaceutical active substances are required to be especially pure substances in order to prevent occurrence of undesirable toxic effects. The substances are purified by a variety of methods such as for the solid substances, among others, thermally induced recrystallization, precipitation with solvents or reagents, extractions and washings, pH regulation, chromatographic methods. The applicants of the patent EP 2533310 purified the finished product by recrystallization of an amphoteric substance from acetonitrile. Subsequent patents such as WO 9310106 and WO 9517396 disclose more complicated and longer processes for affording losartan potassium of high purity which comprise thermally induced crystallization of the amphoteric substance and potassium salt, use of column chromatography and use of adsorptive carriers. The applicants of the patent EP 1106611 and US Pat. No. 6,350,880 report that these methods are unsatisfactory and propose purification

via the salt of losartan with monobasic acids such as chlorides, bromides and *p*-toluenesulfonates. In the final phase, however, it is a single step recrystallization from the acid salt to the alkaline salt with potassium hydroxide resulting in the formation of larger amounts of potassium salt of the anionic moiety of losartan which can be coprecipitated on losartan potassium as impurity, the crystallization itself is carried out in acetonitrile which is not a recommended solvent for the last step because of toxicity.

EP 324377 describes the pharmaceutical compositions wherein 1 to 500 mg of losartan daily is combined with other substances, for example diuretics, and sets forth hypertension as the indication. Patent WO 9219228 discloses optimized compositions of tablets suitable for direct compression.

#### Description of the figures

- Figure 1: DSC curve of a crystalline potassium salt of losartan
- Figure 2: DSC curve of an amorphous potassium salt of losartan
- Figure 3: DSC curve of a crystalline sodium salt of losartan
- Figure 4: DSC curve of an amorphous sodium salt of losartan
- Figure 5: DSC curve of a magnesium salt of losartan
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- Figure 7: IR spectrum of a crystalline potassium salt of losartan
- Figure 8: a section of the IR spectrum shown in Figure 7
- Figure 9: IR spectrum of an amorphous potassium salt of losartan
- Figure 10: a section of the IR spectrum shown in Figure 9
- Figure 11: IR spectrum of a crystalline sodium salt of losartan
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- Figure 13: IR spectrum of amorphous sodium salt of losartan
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- Figure 15: IR spectrum of a magnesium salt of losartan
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- Figure 17: <sup>13</sup>C CP/MAS NMR spectrum of the sample of a crystalline potassium salt of losartan

Figure 18:  $^{13}\text{C}$  CP/MAS NMR spectrum of the sample of an amorphous potassium salt of losartan

Figure 19: X-ray powder diffractogram of a crystalline potassium salt of losartan – form I

Figure 20: X-ray powder diffractogram of an amorphous potassium salt of losartan

Figure 21: X-ray powder diffractogram of a crystalline sodium salt of losartan

Figure 22: X-ray powder diffractogram of an amorphous sodium salt of losartan

Figure 23: X-ray powder diffractogram of a magnesium salt of losartan

Figure 24: X-ray powder diffractogram of a calcium salt of losartan

### Description of the invention

The present invention discloses the formation of completely amorphous forms of alkali and alkali-earth salts, respectively, of losartan without added pharmaceutically acceptable excipients. In our research studies, we have surprisingly found that lyophilization of an aqueous solution of alkali or alkali-earth salt of losartan affords the active substance in the form of fine amorphous powder thus far an unknown form. Using the short and rather rugged method without the long and strictly controlled process of crystallization, losartan potassium with the physicochemical characteristics suitable for incorporation into a pharmaceutical formulation has been obtained in a simple way. An amorphous form often has better bioavailability than a crystalline form, evident from already cited examples for celecoxib [WO 0142221] and some other examples described in US Pat. No. 6,284,277. A problem of unwanted residues of the solvents has been solved in the final phase by using water as the solvent.

For the preparation of the quality salts of losartan for pharmaceutical use highly pure amphoteric losartan is demanded because by lyophilization as an amorphization method the substance cannot be additionally purified. In the preparing quality losartan or highly pure losartan potassium for the preparation of finished pharmaceutical compositions, it has been surprisingly found that effective purification is obtained by conversion *per se* of amphoteric substance – alkali or

alkali-earth salt – amphoteric substance with no need for additional purification of these intermediates by crystallization. The processes *via* the concrete salts provide various degrees of purification, the most effective processes are *via* sodium and potassium salts which are formed as crystalline salts from the solvents.

The process for the preparation of losartan potassium, the object of the present invention, in respect to the known prior art, has an essential advantage because losartan potassium purified *via* these two salts has shown to be purer than losartan potassium prepared according to the disclosure in WO 9310106 and which does not reach the pharmaceutical quality, and no procedure for additional purification of the product is reported in said reference. As evident from the examples, the purification *via* both sodium salt and potassium salt appears to be an effective method since highly pure amphoteric losartan has been obtained from which more pure losartan potassium is prepared than in the prior art described procedure. Surprisingly, the process *via* a sodium salt affords better ruggedness as the influence of pH change on a yield is essentially smaller than in case of preparation of a potassium salt, and a yield *per se* is also better in preparing a sodium salt than in preparing a potassium salt as shown in Table 1.

Purification	<i>via</i> Na salt		<i>via</i> K salt		<i>via</i> Ca salt	
Step	Purity	Yield	Purity	Yield	Purity	Yield
Starting losartan	98.44%		98.44%		98.4%	
Salt	99.42%	82%	99.67%	77%	98.16%	91.9%
Losartan	99.74%	94%	99.82%	93%	98.98%	91.0%
Losartan K	99.91%	94%	99.88%	96%	99.81%	88.9%

**Table 1:** Comparison of the yields and purities of losartan purified *via* different salts

This conversion of the substances affords effective purification and the obtained amphoteric losartan has a low level of impurities and is suitable not only for the preparation of an amorphous potassium salt for pharmaceutical use but also for

the preparation of a crystalline potassium salt for pharmaceutical use, from such amphoteric losartan also the other high-quality alkali and alkali-earth salts of losartan may be prepared.

According to the present invention, the potassium salt of losartan in an amorphous form was prepared from crude losartan by the following process: losartan was first purified by the process in the following steps: losartan dissolved in alcohol was converted to a potassium or a sodium salt of losartan, the resulting salt was isolated in a crystalline form, the resulting isolated salt was dissolved in water or a mixture of water and an organic solvent, an inorganic acid to pH between about 3.6 and about 3.8 was added to the resulting solution, the resulting solution was cooled below about 10°C whereupon losartan precipitated or crystallized and this way obtained losartan was further washed with an organic solvent; further, losartan potassium was prepared in an amorphous form by suspending purified losartan in water, the resulting suspension was dissolved by adding an aqueous solution of potassium hydroxide at a temperature 0 to 30°C until the pH of the solution at least 9.3 was reached; the resulting solution was frozen and in the final step the resulting frozen solution was lyophilized.

The purification process of losartan using the conversion of amphoteric substance – alkali salt or alkali-earth salt – amphoteric substance involves two subprocesses, that is, preparation of the salt and its isolation, and further preparation of amphoteric losartan from said salt.

*Preparation of alkali or alkali-earth salt of losartan and its isolation:*

We have found that according to the first part of the process, alkali or alkali-earth salts of losartan may be prepared if losartan is dissolved in a convenient solvent, for example, in alcohol or a mixtures of alcohol and an aprotic solvent, preferably in *i*-propanol to obtain a concentration of losartan about 170 g/l and at a temperature between about 38°C and about 40°C, an aqueous solution of alkali or alkali-earth metal hydroxide is added to pH between about 9 and about 12.5,

preferably to pH about 10 during over 15 min to about 1 hour, preferably over half an hour, whereupon it is distilled until all azeotropic mixtures are removed.

The procedure for preparation of the alkali-earth salts of losartan was more thoroughly studied and they were prepared by adding nonaqueous alkali-earth metal alcoholate or alkali-earth metal hydroxide to the solution losartan in a suitable solvent or a mixture of solvents, for example in *i*-propanol, prepared to obtain a concentration of about 170 g/l, and the reaction mixture was stirred at elevated temperature between about 40°C and about 85°C, preferably at the reflux temperature.

In all examples the alkali or alkali-earth salts of losartan from the *i*-propanol solution prepared this way were precipitated with a nonpolar solvent, preferably with *n*-heptane at a low temperature, preferably at a temperature below about 10°C and were isolated according to the standard procedures. Crystalline potassium and sodium salts and surprisingly amorphous magnesium and calcium salts result from said preparation. A crystalline potassium salt is in the art known form of losartan, and we have characterized it as a crystal form I but no sodium salt has been characterized yet. Surprisingly, the crystals of losartan sodium appear to be larger and more nicely shaped if a mixture of solvents in which they are formed contains some water. The salts of losartan, according to the present invention, may be also prepared in the form with bound water, which can be influenced by a choice of the conditions, for example pH. Crystalline losartan sodium prepared at pH of about pH 12 retains between about 3.5% and about 4.5% water even after drying and releases water only at a temperature about 100°C.

The preparation of a magnesium salt with magnesium alcoholate, for example with magnesium ethoxide is preferable since the use of magnesium hydroxide because of poor solubility and prevalent conversion to insoluble magnesium oxide is most impractical. Surprisingly, we have found that better results in respect to the yield and quality are also obtained by using sodium or potassium alcoholates in nonaqueous media, for example in alcohol, instead of using aqueous solutions

of sodium or potassium hydroxide, and the process itself is also less time-consuming since it does not require expel of water with azeotropic distillation. The easiest way to obtain the solution of sodium or potassium alcoholate itself is by dissolving commercially available sodium or potassium *t*-butoxide, or by adding metal sodium to alcohol, however, said solution should be prepared just prior to addition of losartan whereas potassium *t*-butoxide may be added directly to the solution of losartan in alcohol. Yield when using a known method with hydroxide is sensitive to pH and presence of water, in said method an impact of these two factors is almost nullified, being particularly evident in the preparation of a potassium salt.

The most convenient process for the preparation of losartan potassium is as follows: losartan is dissolved in a suitable solvent, for example alcohol, preferably *i*-propanol, to obtain a concentration of about 370 g/l and after adding potassium *t*-butoxide, a potassium salt of losartan is separated with the addition of a nonpolar solvent, for example carbon hydride, preferably *n*-heptane, and a yield of separation of the salt from the solution is additionally increased. Losartan potassium is isolated by simple filtration and drying. By this method, analogously a sodium salt of losartan is also prepared using sodium *t*-butoxide in that conversion.

#### *Preparation of losartan from alkali-earth or alkali salts thereof*

According to the purification process of losartan with conversion of amphoteric losartan – alkali salt or alkali-earth salt – amphoteic losartan, further a selected salt, prepared according to one of the described procedures, was dissolved in about 5- to about 20-fold amount of water, preferably to obtain a concentration of about 100 g/l, at a temperature of about 5°C to about 25°C, preferably in a temperature range from 21°C to 25°C, an organic solvent was added, preferably ethyl acetate, and acidified with an inorganic acid, preferably with a concentrated inorganic acid, still more preferably with sulfuric (VI) acid to pH between about 3.6 and about 3.8, preferably to pH about 3.7, thereafter the reaction mixture was

cooled to a temperature of about 0°C to about 15°C, preferably below 10°C and losartan was isolated according to the standard procedures.

*Preparation of amorphous forms of alkali or alkali-earth salts of losartan*

We have found that from the above described processes for the preparation of the salts of losartan, a magnesium salt and calcium salt are amorphous as characterized by X-ray powder analysis. On the other hand, this way isolated potassium salt is a crystal form I which is known in the prior art, and we have found that thus far unknown sodium is also crystalline. Therefore, the method of crystallization of losartan salts from alcohols and another organic solvent cannot be a general method for the preparation of amorphous salts.

In search for a more generalized method for the preparation of amorphous salts of losartan we have found that amorphous forms of alkali or alkali-earth salts of losartan can be prepared by lyophilization according to the following process. Losartan, for example obtained according to the described process, was suspended in water by adding about 5- to about 20-fold amount of water, preferably 10-fold amount of water, at a temperature of about 5°C to about 25°C, preferably at room temperature, an aqueous solution of alkali or alkali-earth metal hydroxide was added, preferably in preparing a potassium salt 10% aqueous solution of potassium hydroxide to pH between about 9 and about 10, preferably to pH about 9.3, whereupon the reaction mixture clarified, the solution was filtered, frozen and lyophilized, that is, the frozen solution was dried under reduced pressure between about 0.1 and 0.01 bar.

If alkali or alkali-earth salts of losartan, suitable and sufficiently pure for pharmaceutical use, are already available amorphous forms thereof may be prepared by lyophilization of their frozen aqueous solutions.

Further, pharmaceutical compositions comprising an alkali or earth-alkali salt of, preferably the potassium salt of losartan in an amorphous form are also the object of the present invention. The pharmaceutical composition can be in a dosage

form suitable for oral or parenteral administration, and is indicated, for example, for the treatment of hypertension, thus, the pharmaceutical composition, the object of said invention, can be, for example, in the form of tablets, capsules, pellets, granules and suppositories. Solid pharmaceutical dosage forms can be coated, for example, to improve pelletability or to adjust disintegration and absorption, respectively.

In concordance with the object of the present invention, we have prepared film coated tablets by the method of the direct dry blend. A blend of losartan potassium with lactose, microcrystalline cellulose, starch and aerosol was prepared and sieved. Magnesium stearate was added and the resulting mixture was rehomogenized. Cores, of 160 mg weight, were compressed into tablets. A film coating prepared as an aqueous suspension from hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol and titanium dioxide was applied onto the cores, and resulting film-coated tablets were polished with talc. Pharmaceutical compositions containing amorphous alkali or alkali-earth salts of losartan may be also prepared by the other convenient methods, for example, by the dry granulation method.

#### Experimental part

The prepared amorphous form of potassium salt of losartan was described and characterized with the following physicochemical methods by comparing the determined properties with in literature available data, that is, with the characteristics of the crystalline salt of losartan prepared according to US Pat. No. 5,608,075 or as described in the examples:

1. Melting point determination
2. Differential thermal calorimetry
3. NMR spectroscopy
4. IR spectroscopy
5. X-ray powder diffraction.

The crystalline potassium salt, prepared according to the processes from the present invention *via* the process of conversion of amphoteric losartan – potassium salt – amphoteric losartan was recognized as form I, and was identical to that prepared according to US Pat. No. 5,608,075. By the above physicochemical methods, the amorphous compound was compared with the crystal forms reported in all other references [US 5608075, Pharm. Res. 10, (1993), 900]; likewise, it was compared with the crystalline sodium salt of losartan prepared according to US Pat. No. 5,608,075.

Sodium, magnesium and calcium salts, thus far unknown in the prior art, were also characterized by the above physicochemical methods. We have found that losartan sodium, prepared according to the above processes and described in detail in the examples, exists in a crystalline form and an amorphous form, losartan calcium and losartan magnesium are identified only in an amorphous form

#### 1. Melting point

The melting point was determined by the method of visual inspection on a microscope with a heated table, and by Thiele method.

The determined melting point of amorphous losartan potassium does not differ essentially from the melting point of crystalline losartan potassium, the samples melt between 226 and 275°C, only the visual processes on an amorphous salt above 200°C are more continuous and more expressed in the sense of sample merging and coloration, on a crystalline salt a more substantially visual change is only at about 230°C, it is the temperature known from the literature as a conversion region to Form II.

A difference between the melting points of crystalline and amorphous losartan sodium is distinct. A crystalline form has a melting point 191–196°C, an and amorphous form 171–177°C.

Melting of calcium and magnesium salts was not observed below 300°C.

## 2. Differential thermal analysis

A differential dynamic calorimeter Perkin Elmer Pyris 1 DSC was used.

Losartan potassium has the first endothermic change above 230°C which would agree with the temperature of conversion of Form I to Form II, known from the literature. Amorphous potassium salt does not have that conversion but essential changes are visible already at a lower temperature thus more extensive exothermic conversion between 190 and 210°C may be observed. Above said temperature considerably sample decomposition and changes are highly visible.

Crystalline losartan sodium has a melting point according to DSC method at 195°C which is concordant to the measurement on Kofler microscope. However, a greater endothermic change may be already observed in the region about 110°C, which is thought to result from the loss of crystal water. Amorphous losartan sodium does not exhibit these changes, conversions above 240°C are characterized by decomposition of the samples. Already above 150°C a very stretched conversion is barely visible, on Kofler microscope observed as a melting-like visible change between 170 and 180°C.

DSC thermograms of the samples of losartan sodium and losartan magnesium are similar to the thermograms of amorphous losartan sodium at temperatures above 200°C, only decomposition of the samples is observed in the approximately same temperature region with somewhat different dynamics of thermal fluxes.

DSC thermograms are shown in Figures 1 to 6.

## 3. Solid-state $^{13}\text{C}$ CP/MAS NMR spectroscopy

A Varian spectrometer INOVA 600 at 150 kHz was used for scanning of the samples by the  $^{13}\text{C}$ -NMR Solid-State CP-MAS method. The samples were measured with TOSS at spinning 10 kHz, pulse (90) 4.4  $\mu\text{s}$ .

Two forms of potassium salt of losartan were recorded. Crystalline potassium salt exhibits sharp peaks, amorphous potassium salt exhibits a broader signal, whereat some of them are merged with a neighbouring peak or absent. The spectra are shown Figures 17 and 19, and a record of chemical shifts in Table 2:

Crystalline losartan potassium (ppm)	Amorphous losartan potassium (ppm)
14.1	13.8
17.1	/
21.0	22.3
27.8	26.8
30.4	29.0
/	47.1 (wide)
50.0 (wide)	52.0 (wide)
123.8	/
126.5	127.4
130.3	129.2
131.7	merged
134.6	/
136.1	135.6
141.7	140.9
146.6	/
148.1	148.7
163.0	162.4

**Table 2:** Chemical shifts of the solid-state samples of losartan potassium scanned by NMR CP/MAS method

From the table it is evident that an amorphous form is characterized by absence of the peaks 146.6, 134.6 and 17.1 ppm and presence of a wide peak at 47.1 ppm, in case of the other peaks there are smaller shifts in both directions, broadening of lines and for merging of several peaks into a group.

#### 4. IR (infrared) spectroscopy

An infrared spectrometer »Bio-Rad FTS-60, Digilab-Division« was used.

Recorded IR spectra are illustrated in Figures 7 to 14, the most distinct absorption peaks are between 1510 and 700  $\text{cm}^{-1}$  and are also shown in the table below,

while the values for form II of crystal salt are taken from the literature [Pharm. Res. 10 (1993), 900]:

Crystalline losartan potassium form I)	Crystalline losartan potassium (form II)	Crystalline losartan sodium	Amorphous losartan sodium	Losartan magnesium	Losartan calcium
1507		1507	1507	1507	1508
1497		1498	1494	1495	1494
1472		1474	/	/	/
1460		1461	1460	1461	1461
1423		1426	1425	1426	1426
1406		1408	1408	1409	1409
1378		weak	1380	1380	1380
1358	1357	1360	1358	1359	1358
1342	/	1342	/	/	/
1260		1264	1256	1258	1258
/		1140	1144	1150	1148
1133		1132	merged	merged	merged
1113		1109	1108	1108	1108
1074		1080	1074	1075	1075
/		1011	1013	1014	1014
1008		1008	1006	1006	1006
996		/	/	/	/
954	/	958	954	953	954
/		949	/	/	/
934	940	937	933	934	934
886	/	/	weak	weak	878
844		/	/	/	/
841		839	/	/	/
826		820	824	824	824
789		785	787	787	786
763	754	753	761	760	760
merged with 763		740	743	merged with 760	743
713	/	weak	weak	714	714

**Table 3:** Characteristic bands [ $\text{cm}^{-1}$ ] in the IR spectra of different salts of losartan in the region between  $1550$  and  $700 \text{ cm}^{-1}$

The IR spectra of an amorphous and a crystalline potassium salt differ essentially more or less over the entire scale primarily in the shapes of absorption bands and minor shifts in the values of absorption peaks, however, the most evident characteristic in the IR spectrum of an amorphous potassium salt is the absence of absorption peaks at  $1472 \pm 5$ ,  $1342 \pm 5$  and between  $835$  and  $845 \text{ cm}^{-1}$ . On the

other hand, an amorphous form distinguishes from Form II by the presence of the bands which are absent in said crystal form, these are the regions  $954 \pm 5$ ,  $949 \pm 5$ ,  $870\text{--}890$  and  $715 \pm 5 \text{ cm}^{-1}$ .

The IR spectrum of crystalline losartan sodium is more similar to losartan potassium of form I than to amorphous losartan sodium, however it is evidently distinct from a potassium salt by the absence of the peaks at the intervals of the wave-numbers  $995\text{--}1000$  and  $870\text{--}890 \text{ cm}^{-1}$  and changes in the region between  $820$  and  $850 \text{ cm}^{-1}$ , identified by the presence of the peaks  $839 \pm 1$  and  $820 \pm 1 \text{ cm}^{-1}$ . Amorphous losartan sodium distinguishes from crystalline losartan sodium by the absence of the peaks in the regions of the wave-numbers  $1472 \pm 5$ ,  $1342 \pm 5$  and between  $835$  and  $845 \text{ cm}^{-1}$ .

All amorphous forms of losartan salts, both potassium, sodium, magnesium or calcium, have an equivalent IR spectrum, differences are within an error of analytical and software perception of the wave-number value of the band peak and differ from the other crystalline salts by the absence of the absorption bands in the regions of the wave-numbers  $1472 \pm 5$ ,  $1342 \pm 5$  and between  $835$  and  $845 \text{ cm}^{-1}$ . This may be explained that there are no specific bands in the spectrum which would result from the influence of cations on the energy states of bonding, and the other bands are a result of interior molecular events because intermolecular influences due to an unordered amorphous state are dispersed and thus undistinguishable in an IR spectrum.

## 5. X-ray powder analysis

The samples were recorded on an apparatus Philips PW1710 using the reflexion technique under the conditions:  $\text{CuK}\alpha$  radiation, range from  $2^\circ$  to  $37^\circ 2\theta$  with  $0.04^\circ 2\theta$  step, integration time 1 second.

In amorphous losartan potassium, the X-ray powder diffractograms of losartan potassium indicate the absence of discrete diffractions characteristic of crystal

forms and continuous diffraction over the entire recorded region which is an indisputable confirmation of the amorphous structure of the material contrary to the crystalline sample which indicates characteristic bands at the angles which in the prior art are characteristic for polymorph form I. Both diffractograms are shown in Figures 19 and 20.

In amorphous losartan sodium, the X-ray powder diffractograms of losartan sodium indicate the absence of diffractions and an indisputably amorphous structure of the material contrary to the crystalline sample which shows sharp peaks which indicate high crystallinity. Both diffractograms are shown in Figures 21 and 22.

The X-ray powder diffractograms of losartan magnesium and losartan calcium indicate an evident amorphous structure of the samples irrespective of the mode of their preparation. The diffractograms of typical samples of magnesium and calcium salts are shown Figures 23 and 24.

In the following examples which further illustrate but in no way limit the present invention, the best modes of the preparation of novel pharmaceutically useful forms of losartan including new methods of purification and isolation according to the present invention are presented.

#### **Example 1**

Losartan crude (2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(1H-tetrazol-5-yl)-biphenyl-4-yl] methyl]-1H-imidazole)

A blend of 129.80 g of 5-[2-(4'-bromomethylbiphenyl)]-2-triphenylmethyl-2H-tetrazole, 43.4 g of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1H-imidazole and 38.27 g of potassium carbonate in 550 ml of N,N-dimethylacetamide was mixed at a temperature of 0–5°C for 8 hours and at room temperature overnight. To the mixture 8.02 g of NaBH<sub>4</sub> and 18 ml of water was added, cooled to room temperature and stirred for 3 hours. The reaction mixture while stirring vigorously

was poured into 1.1 l of water and filtered, the precipitate was washed with 550 ml of water, dried *in vacuo* at room temperature over silica gel.

2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(triphenylmethyl-2H-tetrazol-5-yl)[1,1'biphenyl-4-yl] methyl]imidazole was obtained which was recrystallized from chlorobutane and ethyl acetate to yield 66.77 g after the final reaction and purification after drying.

To a solution of 67.77 g of 2-*n*-butyl-4-chloro-5-hydroxymethyl-1-[[2'-(triphenylmethyl-2H-tetrazol-5-yl)[1,1'biphenyl-4-yl]methyl]imidazole in 316 ml of tetrahydrofuran (THF) while stirring 105.9 g of 12% HCl was added at a temperature of 23°C over one hour. The mixture was stirred at room temperature overnight. 30% of NaOH was added a temperature to 22°C over one hour until the pH of 12.5 (ca. 100 ml) was attained. THF was evaporated at a temperature of 60°C and demineralized water was added to the original volume. The precipitate formed was filtered, washed with 2 x 50 ml of demineralized water and discarded. The water phase was extracted with 1 x 50 ml of toluene. The organic layer was separated and 124 ml of ethyl acetate was added to the water phase. The reaction mixture while stirring vigorously was acidified with concentrated H<sub>2</sub>SO<sub>4</sub> at a temperature 21–25°C to pH 3.6–3.8, cooled below 10°C and stirred for 1 hour. The produced precipitate was filtered, washed with 130 ml of ethyl acetate, filtered again and dried *in vacuo* at a temperature of 50°C overnight to yield 40.8 g of losartan in an amphoteric form.

## Example 2

### Formation of a sodium salt of losartan – method 1

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added the solution of 5.5 g of sodium hydroxide in 5.7 ml of water at a temperature 38–40°C to pH 12 over half an hour. Approximately 35 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 140 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting

precipitate was diluted with 55 ml of *n*-heptane, filtered, washed with 110 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 35.0 g of a sodium salt of losartan.

Melting point: 191–196°C

Water according to Karl-Fisher: 4.2%.

Assay of sodium 4.4% (5.0% calculated to the dry matter)

### Example 3

Formation of a sodium salt of losartan – method 2

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added the solution of 5.5 g of sodium hydroxide in 5.7 ml of water at a temperature 38–40°C to pH 12 over half an hour. Approximately 35 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 140 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 55 ml of *n*-heptane, filtered, washed with 110 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 37.0 g of sodium salt of losartan.

Melting point: 190–198°C

Water according to Karl-Fisher: 0.3%.

### Example 4

Formation of sodium salt of losartan – method 3

To 40.81 g of losartan from Example 1 in 120 ml of *i*-propanol was added 9.28 g of sodium *t*-butoxide. The reaction mixture was clarified. 145 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was filtered and washed with 165 ml *n*-heptane, dried at 40°C *in vacuo* to yield 37.0 g of a sodium salt of losartan.

Melting point: 191–196°C

Assay of sodium 4.7% (5.2% calculated to the dry matter).

**Example 5**

Formation of a potassium salt of losartan – method 1

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added the solution of 5.5 g of potassium hydroxide in 5.7 ml of water at a temperature 38–40°C to pH 12 over half an hour. Approximately 35 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 141.5 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 54 ml of *n*-heptane, filtered, washed with 108 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 21.36 g of losartan potassium.

**Example 6**

Formation of a potassium salt of losartan – method 2

To 10.2 g of losartan from Example 1 in 59 ml of *i*-propanol was added the solution of 1.4 g of potassium hydroxide in 1.5 ml of water a temperature 38–40°C to pH 10 over half an hour. Approximately 19 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 36 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 14 ml of *n*-heptane, filtered, washed with 26 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 8.57 g of losartan potassium.

**Example 7**

Formation of a potassium salt of losartan – method 3

To 40.81 g of losartan from Example 1 in 110 ml of *i*-propanol was added 10.86 g of potassium *t*-butoxide a temperature between 10°C and 25°C. The reaction mixture was clarified whereupon a dense white precipitate was formed. 150 ml of *n*-heptane was added and stirred at room temperature for 1 hour. It was filtered

and washed with 75 ml of *n*-heptane, dried at 50°C *in vacuo* overnight to yield 43.25 g of losartan potassium.

### Example 8

Formation of a magnesium salt of losartan

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added 6.07 g of magnesium ethoxide and stirred at the reflux temperature overnight. It was hot filtered, 650 ml of *n*-heptane was added and cooled to room temperature to precipitate the product. It was filtered and washed with 110 ml of *n*-heptane, and dried *in vacuo* at 50°C to yield 37.9 g of a magnesium salt of losartan.

Melting point: above 300°C

Assay of magnesium 2.9% (3.2% calculated to the dry matter).

### Example 9

Formation of a calcium salt of losartan

To 40.81 g of losartan from Example 1 in 235 ml of *i*-propanol was added 3.92 g of calcium hydroxide and stirred at the reflux temperature for 1 hour, and hot filtered. 410 ml of *n*-heptane was added to the filtrate and cooled to room temperature. The solvent was decanted from a resinous residue and 820 ml *n*-heptane was added. It was stirred until a white precipitate was crystallized which was filtered, washed with 110 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 39.2 g of a calcium salt of losartan.

Melting point: above 300°C

Assay of calcium 4.0% (4.7% calculated to the dry matter).

### Example 10

Losartan purified – method 1

35 g of sodium salt of losartan was dissolved in 350 ml of water, 106 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with

concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 120 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 29.3 g of losartan.

#### **Example 11**

Losartan purified – method 2

42.66 g of a potassium salt of losartan was dissolved in 430 ml of water, 130 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 145 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 36.6 g of losartan.

#### **Example 12**

Losartan purified – method 3

37.9 g of a magnesium salt of losartan was dissolved in 388 ml of demineralized water, 120 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 130 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 32.3 g of losartan.

#### **Example 13**

Losartan purified – method 4

38.0 g of a calcium salt of losartan was dissolved in 380 ml of water, 115 ml of ethyl acetate was added and acidified at a temperature 21 to 25°C to pH 3.6–3.8 with concentrated sulfuric acid, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 130 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C over night to yield 36.2 g of losartan.

**Example 14**

Preparation of pharmaceutically usable losartan potassium *via* crystalline losartan sodium

To 20.4 g of crude losartan (chromatographic purity 98.73%) in 120 ml of *i*-propanol was added the solution of 2.75 g of sodium hydroxide in 2.9 ml of water at a temperature 38–40°C to pH 10 over half an hour. Approximately 18 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 70 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 28 ml of *n*-heptane, filtered, washed with 55 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 18.5 g of a crystalline sodium salt of losartan (yield: 87%, chromatographic purity: 99.42%).

The substance obtained was dissolved in 185 ml of water, 56 ml of ethyl acetate was added and acidified at a temperature 21–25°C to pH 3.6–3.8 with concentrated sulfuric acids, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 64 ml of ethyl acetate, filtered again and dried *in vacuo* at a temperature 50°C overnight to yield 16.5 g of losartan (yield of the phase: 94%, chromatographic purity: 99.74%).

The resulting product was dissolved in 45 ml of *i*-propanol, 4.39 g of potassium *t*-butoxide between 10°C and 25°C was added. The reaction mixture clarified itself whereupon a dense, white precipitate was formed. 60 ml of *n*-heptane was added and stirred at room temperature for 1 hour. It was filtered and washed with 30 ml of *n*-heptane, dried *in vacuo* at 50°C overnight to yield 16.9 g of losartan potassium (yield of the phase: 94%, chromatographic purity: 99.91%, overall yield: 77%).

**Example 15**

Preparation of pharmaceutically usable losartan potassium *via* crystalline losartan potassium

As already described in Example 1, to 10.2 g of crude losartan from Example 14 (chromatographic purity 98.73%) in 59 ml of *i*-propanol was added the solution of 1.4 g of potassium hydroxide in 1.5 ml of water at a temperature 38–40°C to pH 10 over half an hour. Approximately 19 ml of the azeotropic mixture *i*-propanol / water was removed by distillation. 36 ml of *n*-heptane was added and stirred at room temperature until a white precipitate was formed. The resulting precipitate was diluted with 14 ml of *n*-heptane, filtered, washed with 26 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 8.57 g of losartan potassium (yield: 77%, chromatographic purity: 99.67%).

The resulting potassium salt of losartan was dissolved in 86 ml of water, 26 ml of ethyl acetate was added and acidified at a temperature 21–25°C to pH 3.6–3.8 with concentrated sulfuric acids, cooled below 10°C and stirred for 1 hour. The formed precipitate was filtered, washed with 29 ml of ethyl acetate, filtered again and dried *in vacuo* at 50°C overnight to yield 7.35 g of losartan (yield of the phase: 93%, chromatographic purity: 99.82%).

The resulting product was dissolved in 20 ml of *i*-propanol, 1.96 g of potassium *t*-butoxide in a temperature range between 10°C and 25°C was added. The reaction mixture clarified whereupon a dense, white precipitate was formed. 27 ml of *n*-heptane was added and stirred at room temperature for 1 hour, filtered and washed with 13 ml of *n*-heptane, dried *in vacuo* at 50°C overnight to yield 7.66 g of losartan potassium (yield of the phase: 96%, chromatographic purity: 99.88%, overall yield: 69%).

**Example 16**

Comparative example of the preparation of a potassium salt according to known prior art

To 40.81 g of losartan (chromatographic purity 98.73%) in 153 ml of *i*-propanol was added the mixture of 10 g of potassium hydroxide, 5.1 ml of water and 100 ml of *i*-propanol at a temperature 38–40°C to pH 10–11 over half an hour. Approximately 140 ml of the solvent (*i*-propanol / water mixture) was removed by distillation and 92 ml of *n*-heptane was added. It was stirred at room temperature until a white precipitate was formed. The precipitate was diluted with 54 ml of *n*-heptane, filtered, washed with 70 ml of *n*-heptane and dried *in vacuo* at 50°C to yield 38.4 g of losartan potassium (yield: 86%, chromatographic purity: 99.67%).

**Example 17**

An amorphous potassium salt of losartan – method 1

29.3 g of purified losartan from one of Examples 8 to 11 was suspended in 293 ml of water. At room temperature the pH was adjusted to 9.3 with 10% an aqueous potassium hydroxide solution. The reaction mixture clarified. The solution was filtered and lyophilized to yield 31.8 g of white, completely amorphous product losartan potassium.

**Example 18**

An amorphous potassium salt of losartan – method 2

20.0 g of a crystalline potassium salt of losartan was dissolved in 200 ml of distilled water. The clear solution was filtered and lyophilized to yield 20.0 g of an amorphous potassium salt of losartan.

**Example 19**

An amorphous sodium salt of losartan – method 1

5.0 g of purified losartan from one of Examples 8 to 11 was suspended in 50 ml of water. At room temperature the pH was adjusted to 9.62 with 10% aqueous sodium hydroxide solution. The reaction mixture clarified. The solution was filtered and lyophilized to yield 5.2 g of an amorphous sodium salt of losartan.

#### **Example 20**

An amorphous sodium salt of losartan – method 2

3.10 g of crystalline losartan sodium was dissolved in 31 ml of water. The clear solution was filtered and lyophilized to yield 3.10 g of an amorphous sodium salt of losartan.

Melting point: 171–177 °C

#### **Example 21**

A solid pharmaceutical composition containing a potassium salt of losartan

Film coated tablets were prepared containing in the core:

losartan potassium	50.00 mg
lactose monohydrate	28.52 mg
microcrystalline cellulose	60.00 mg
pregelatinized starch	20.00 mg
aerosil	0.48 mg
magnesium stearate	1.00 mg

For film coating the following was used:

hydroxypropylmethylcellulose	1.984 mg
hydroxypropylcellulose	0.496 mg
polyethylene glycol	0.400 mg
titanium dioxide	0.920 mg
talc	0.200 mg

The tablets were prepared by the direct dry blend procedure. The blend of the active substance with lactose, microcrystalline cellulose, starch and aerosol was prepared and the mixture was sieved. Magnesium stearate was added and all together rehomogenized. The cores weighing 160 mg were compressed into

tablets. The film coating prepared as a suspension in demineralized water from the listed ingredients was applied onto the cores. The coated tablets were polished with talc.

### Example 22

A solid pharmaceutical composition containing a potassium salt of losartan and hydrochlorothiazide

Tablets containing in the core:

losartan potassium	50.00 mg
hydrochlorothiazide	12.50 mg
lactose monohydrate	26.90 mg
microcrystalline cellulose	60.00 mg
pregelatinized starch	23.60 mg
aerosil	0.50 mg
magnesium stearate	1.50 mg

and the coating:

hydroxypropylmethylcellulose	1.925 mg
hydroxypropylcellulose	1.925 mg
titanium dioxide	1.130 mg
iron oxide E 172	0.020 mg

were prepared by the dry granulation method by slugging. The active substances losartan potassium and hydrochlorothiazide were mixed with starch and aerosol first, and the mixture was sieved. Lactose, microcrystalline cellulose and the remaining quantity of aerosol were added, sieved, and the mixture was slugged. The slugs were ground, magnesium stearate was added and the granulation homogenized. The cores weighing 175 mg were compressed into tablets. The film coating prepared as a suspension in demineralized water from the listed ingredients was applied onto the cores. The film coated tablets were polished with talc.

Claims

1. Alkali or alkali-earth metal salts of losartan in an amorphous form.
2. The alkali salt of losartan according to claim 1 characterized in that it is selected between a sodium salt of losartan in an amorphous form or a potassium salt of losartan in an amorphous form.
3. The potassium salt of losartan in an amorphous form according to claim 2 characterized in that its X-ray powder diffractogram does not have discrete diffractions, range from  $2^{\circ}$  to  $37^{\circ} 2\theta$ .
4. The potassium salt of losartan in an amorphous form according to claim 2 characterized with continuity of diffraction on its X-ray powder diffractogram shown in *Figure 20*.
5. The potassium salt of losartan in an amorphous form according to claim 2 characterized in that its IR spectrum does not exhibit characteristic absorption bands at the wave numbers about  $1472 \pm 5 \text{ cm}^{-1}$ , about  $1342 \pm 5 \text{ cm}^{-1}$  and between about  $835 \text{ cm}^{-1}$  and about  $845 \text{ cm}^{-1}$ .
6. A process for the preparation of alkali or alkali-earth salts of losartan in an amorphous form.
7. The process according to claim 6 characterized in that an alkali salt of losartan in an amorphous form is selected between a sodium salt of losartan in an amorphous form or a potassium salt of losartan in an amorphous form; an alkali-earth salt of losartan in an amorphous form is selected between a magnesium salt of losartan in an amorphous form or a calcium salt of losartan in an amorphous form.
8. The process according to claims 6 and/or 7 characterized in that the final step of the process is lyophilization of the frozen aqueous solution of an alkali or alkali-earth salt of losartan.

9. The process according to claims 6 and/or 7 which comprises the following steps:
  - a) freezing of the solution of an alkali or alkali-earth salt of losartan;
  - b) lyophilizing of the resulting frozen solution.
10. The process according to claim 9 characterized in that an alkali salt of losartan in an amorphous form is a potassium salt of losartan in an amorphous form and a solution of the alkali salt of losartan is an aqueous solution of a potassium salt of losartan.
11. The process according to claim 10 wherein the preparation of the aqueous solution of a potassium salt of losartan comprises the following steps:
  - a) suspending of losartan in water;
  - b) dissolving of the resulting suspension by adding an aqueous solution of potassium hydroxide at a temperature from 0° to 30°C until pH of the solution of at least about 9.3 is attained.
12. The process according to any of claims 6 to 11 characterized in that alkali or alkali-earth salts of losartan in an amorphous form are prepared from losartan purified by the process comprising the following steps: conversion of losartan to the salt; further isolation of said salt; conversion of the salt to losartan.
13. The process according to any of claims 6 to 11 characterized in that alkali or alkali-earth salts of losartan in an amorphous form are prepared from losartan purified by the process comprising the following steps:
  - a) conversion of losartan to an alkali or alkali-earth salt of losartan;
  - b) isolation of the resulting salt of losartan;
  - c) conversion of the isolated salt to losartan by acidifying with an inorganic acid in an organic solvent.
14. The process according to any of claims 6 to 9 characterized in that alkali or alkali-earth salts of losartan in an amorphous form are prepared from losartan purified by the process comprising the following steps:
  - a) conversion of losartan to a potassium or sodium salt of losartan;
  - b) isolation of the resulting salt of losartan in a crystal form;

- c) dissolving of the resulting isolated salt in water or a mixture of water and an organic solvent;
  - d) addition of an inorganic acid to the resulting solution to pH between about 3.6 and about 3.8;
  - e) cooling of the resulting solution below about 10°C whereupon losartan is precipitated;
  - f) washing of the resulting precipitated losartan with an organic solvent.
15. The process according to claims 10 and/or 11 characterized in that a potassium salt of losartan in an amorphous form is prepared from losartan purified by the process comprising the following steps:
- a) conversion of losartan to a potassium or sodium salt of losartan;
  - b) isolation of the resulting salt of losartan in a crystal form;
  - c) dissolving of the isolated salt in water or a mixture of water and an organic solvent;
  - d) addition of an inorganic acid to the resulting solution to pH between about 3.6 and about 3.8;
  - e) cooling of the resulting solution below about 10°C whereupon losartan is precipitated;
  - f) washing of the resulting precipitated losartan with an organic solvent.
16. The process according to claims 14 and/or 15 characterized in that the conversion of losartan to a potassium salt and its isolation in the purification process comprises the following steps:
- a) addition of a sodium alcoholate to a solution of losartan in alcohol or in a mixture of alcohol and an aprotic solvent;
  - b) precipitation or crystallization of the resulting salt;
  - c) isolation of the resulting precipitate or crystallized salt by filtration or centrifuging.
17. The process according to claims 14 and/or 15 characterized in that the conversion of losartan to a sodium salt and its isolation in the purification process comprises the following steps:

- a) addition of a sodium alcoholate or sodium hydroxide to a solution of losartan in alcohol or in a mixture of alcohol and an aprotic solvent to pH between about 9 and about 12;
  - b) precipitation or crystallization of the resulting salt;
  - c) isolation of the resulting precipitate or crystallized salt by filtration or centrifuging.
18. The process according to any of claims 13 to 15 characterized in that an inorganic acid is sulfuric (VI) acid.
19. The process according to any of claims 13 to 15 characterized in that an organic solvent is ethyl acetate.
20. The use of crystal alkali or alkali-earth salt of losartan in the process for the preparation of an alkali or alkali-earth salt of losartan in an amorphous form according to any of claims 12 to 19.
21. The use of crystal sodium salt of losartan in the process for the preparation of a potassium salt of losartan in an amorphous form according to any of claims 12, 13, 14, 15, 17, 18, 19.
22. The pharmaceutical composition containing an alkali or alkali-earth salt of losartan in an amorphous form as the active substance and pharmaceutically acceptable excipients.
23. The pharmaceutical composition according to claim 22 characterized in that the active substance is selected between a potassium salt of losartan in an amorphous form or a sodium salt of losartan in an amorphous form.
24. The use of the alkali or alkali-earth salt of losartan in an amorphous form for the preparation of a medicament.
25. The use of the alkali or alkali-earth salt of losartan in an amorphous form for the preparation of a medicament for the treatment of hypertension.
26. The use of the alkali or alkali-earth salt of losartan in an amorphous form for the preparation of a medicament for the treatment of hypertension according to

claim 25 characterized in that said salt is a potassium salt of losartan in an amorphous form.

Lek Pharmaceuticals d.d.

## Abstract

Pharmaceutically suitable amorphous alkali and earth alkali salts of 2-*n*-butyl-4-kloro-5-hidroksimetil-1-[[2'-(1H-tetrazol-5-il)[1,1'-bifenil]-4-il]metil]-1H-imidazole were prepared by lyophilisation of an aqueous solution of its salt prepared from losartan, which can be conveniently purified by transition amphoteric - alkali and earth alkali salts – amphoteric.

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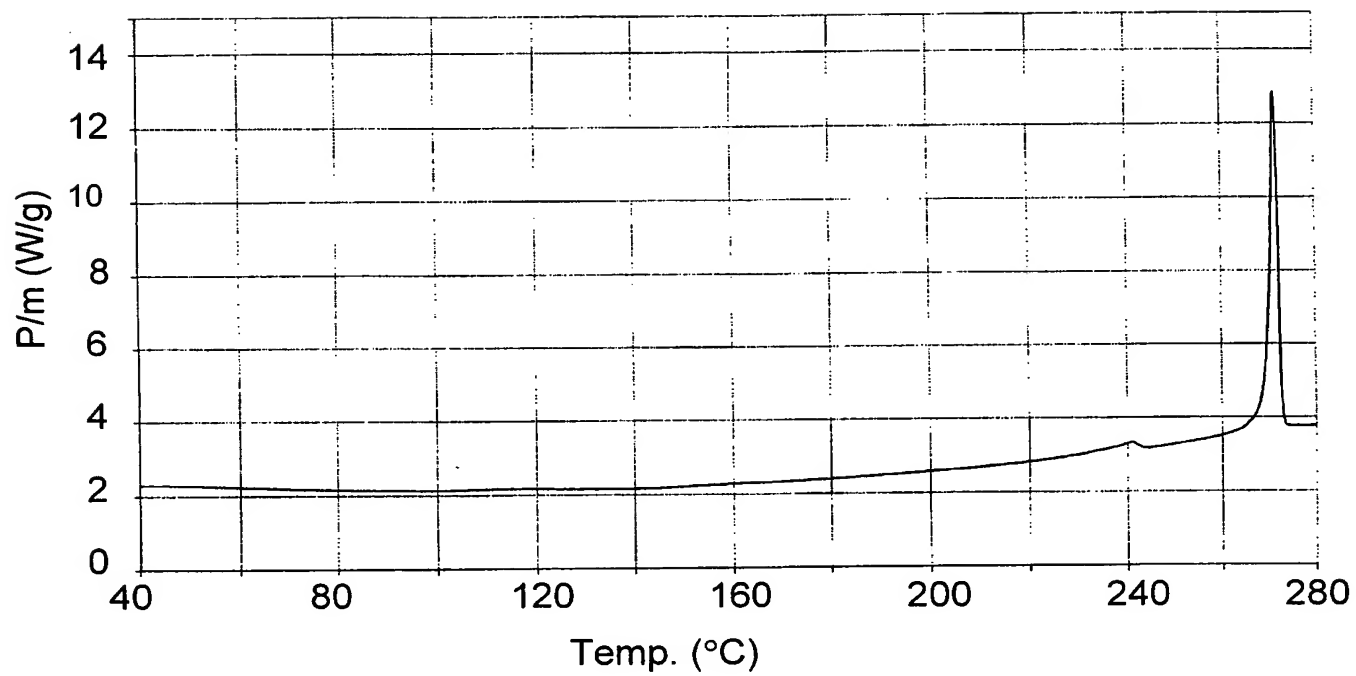


Figure 1

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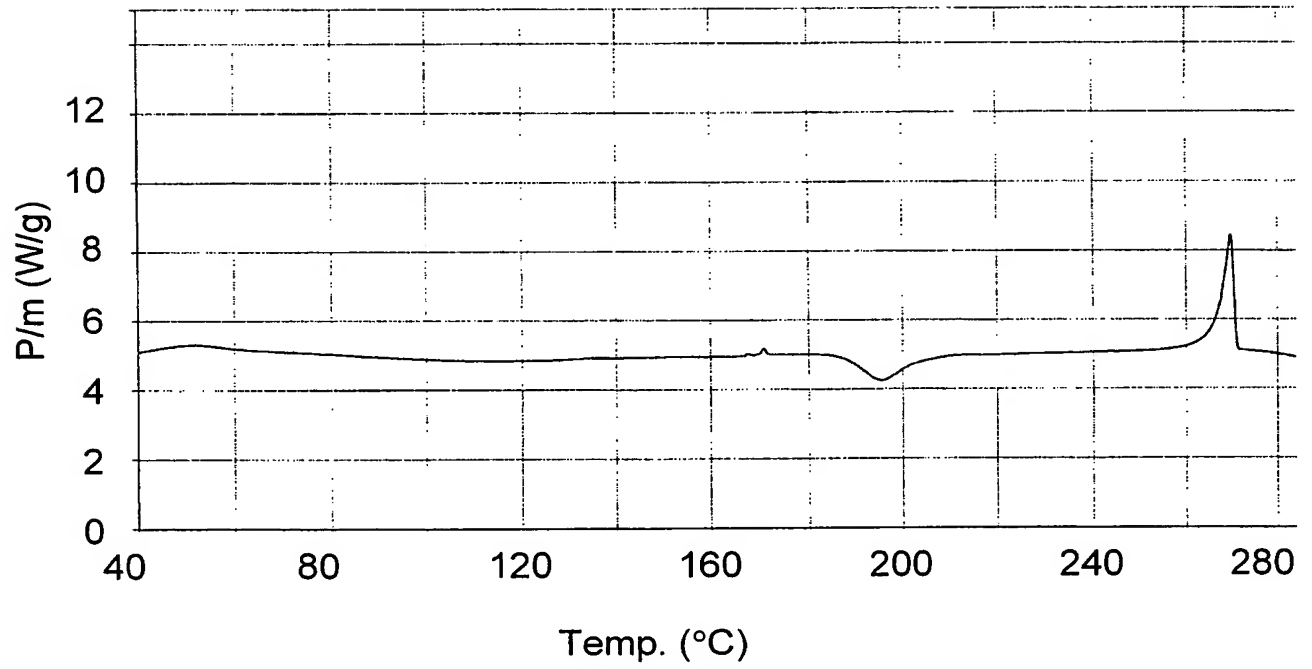


Figure 2

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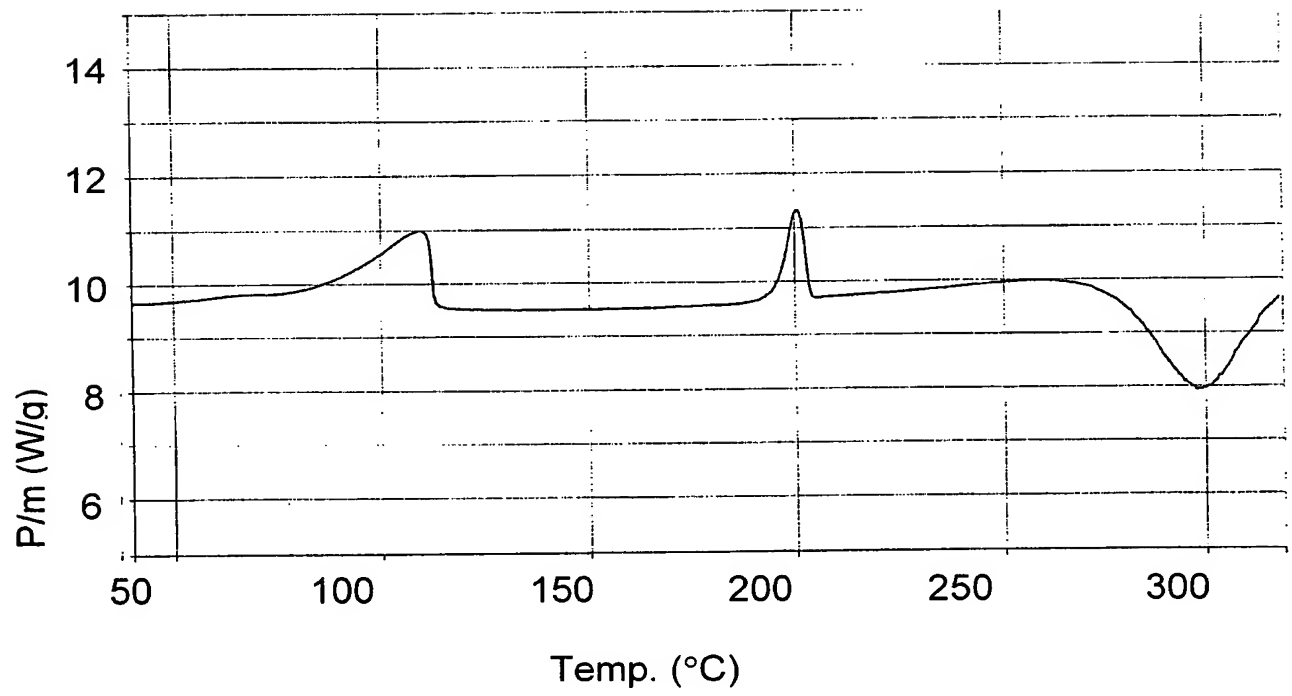


Figure 3

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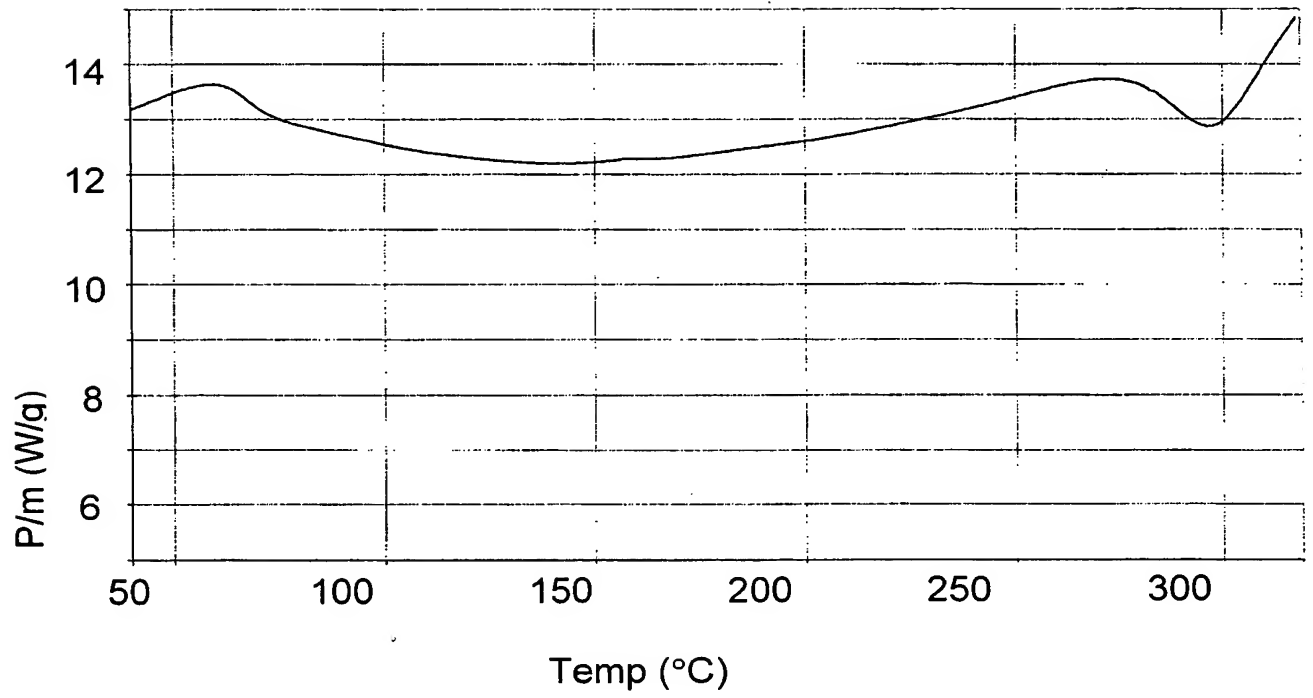


Figure 4

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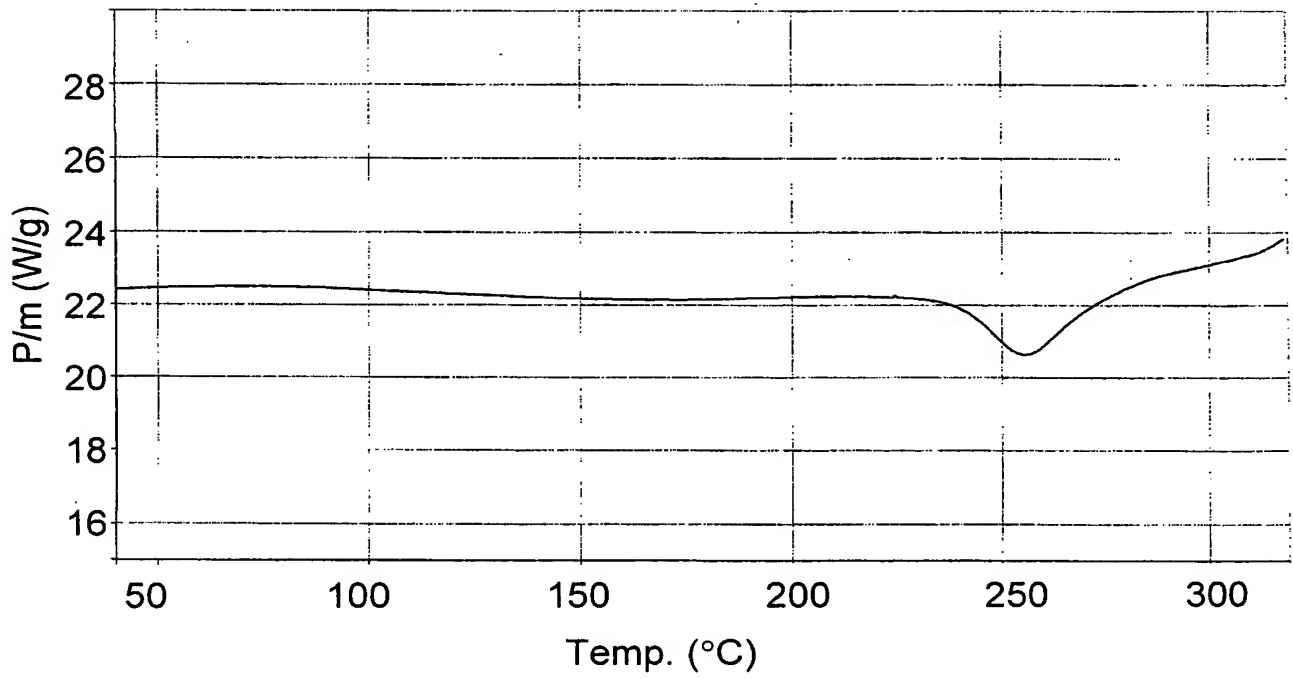


Figure 5

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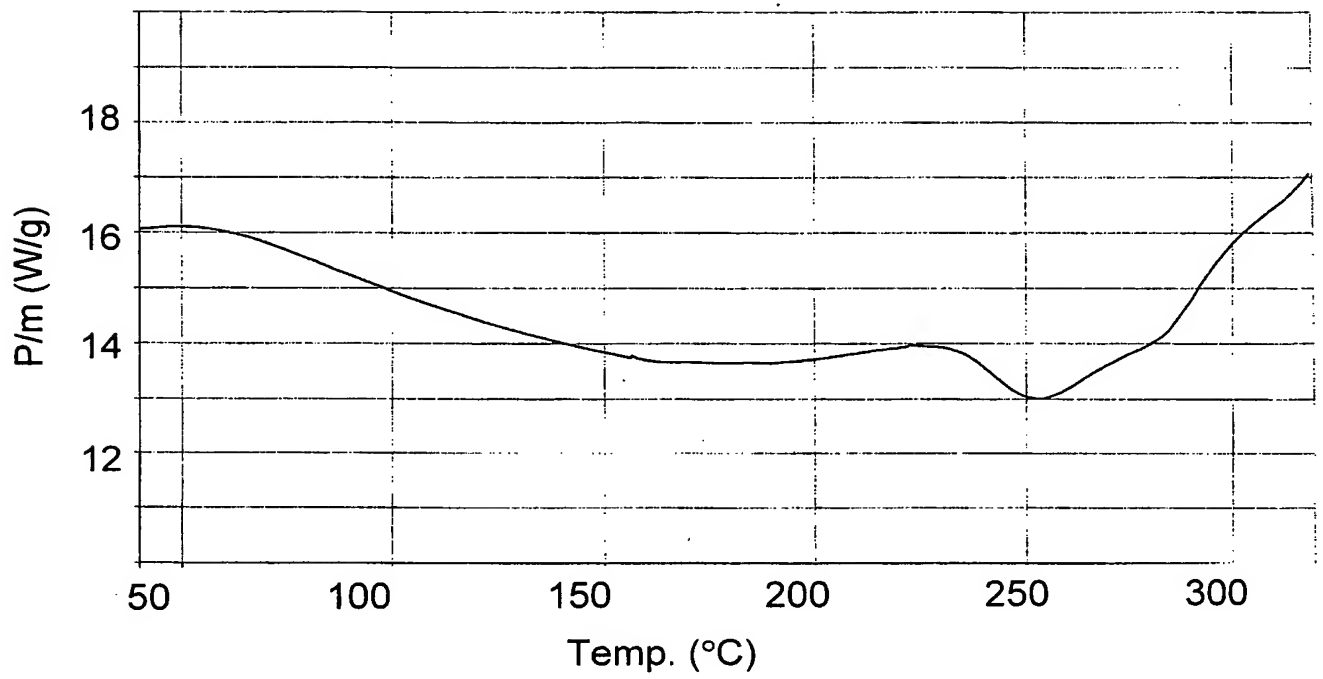


Figure 6

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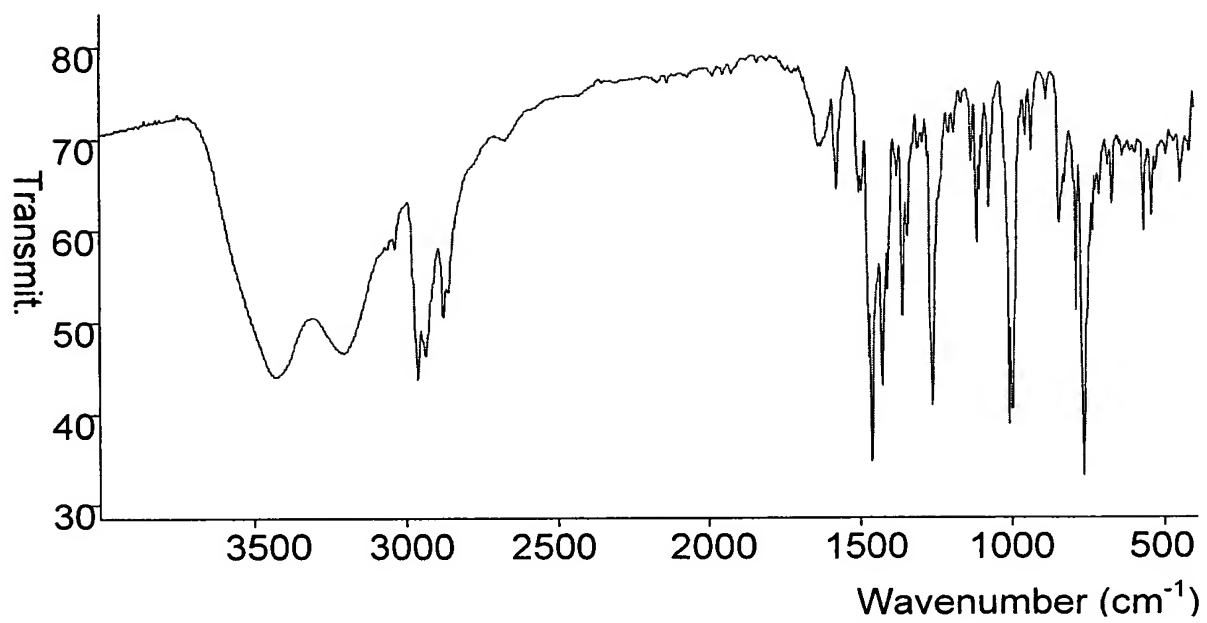


Figure 7

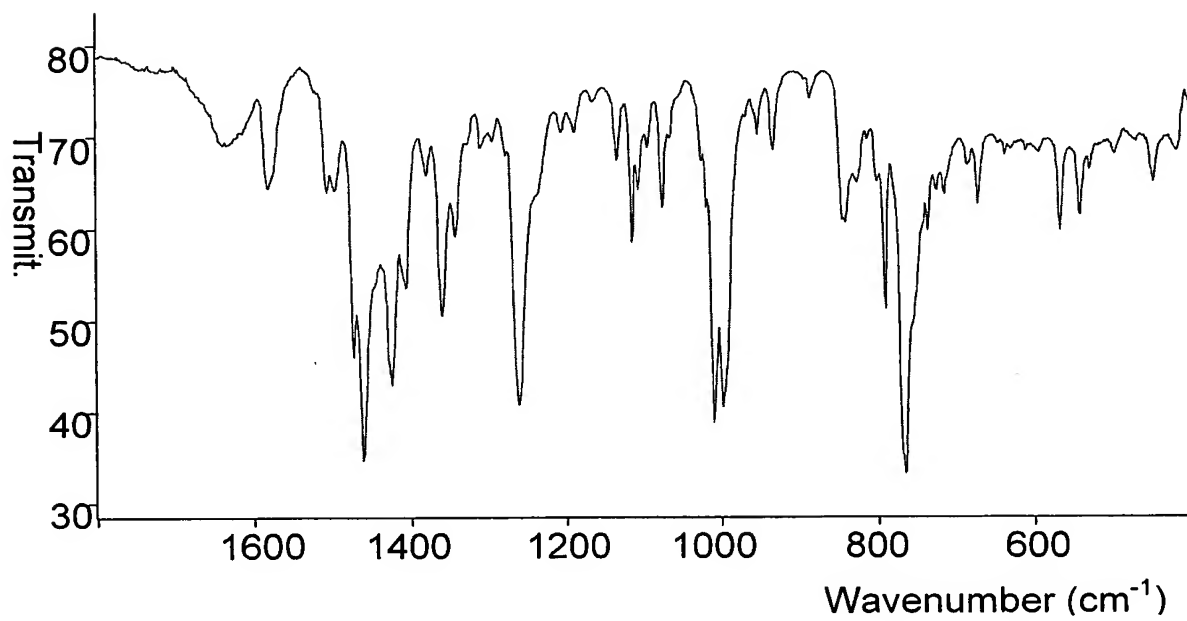


Figure 8

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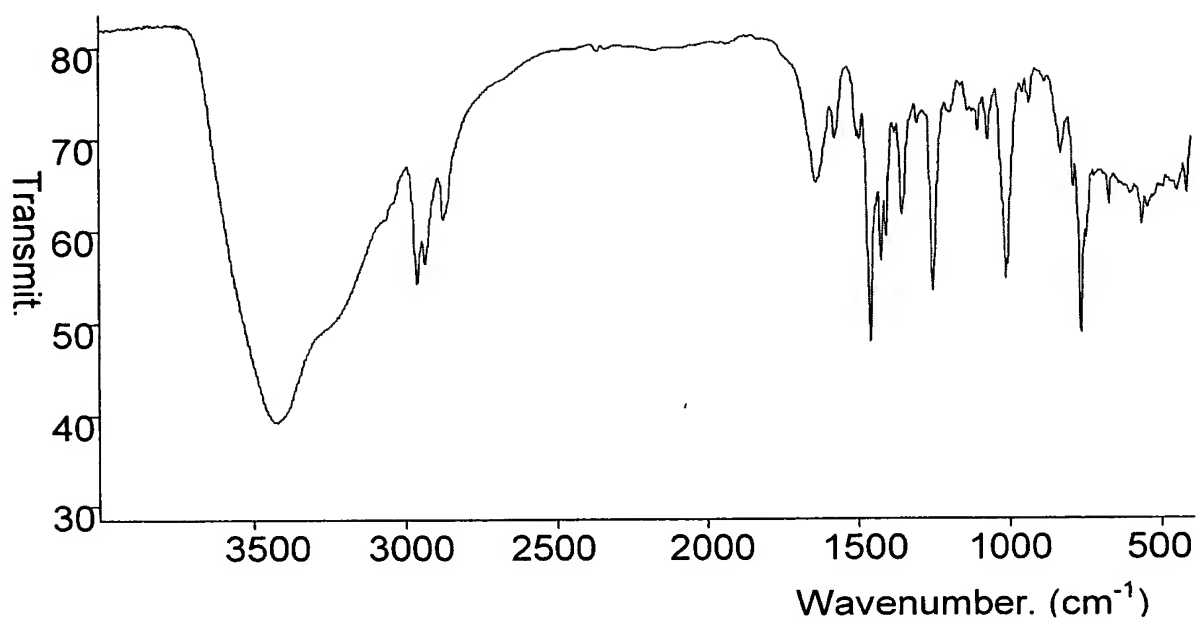


Figure 9

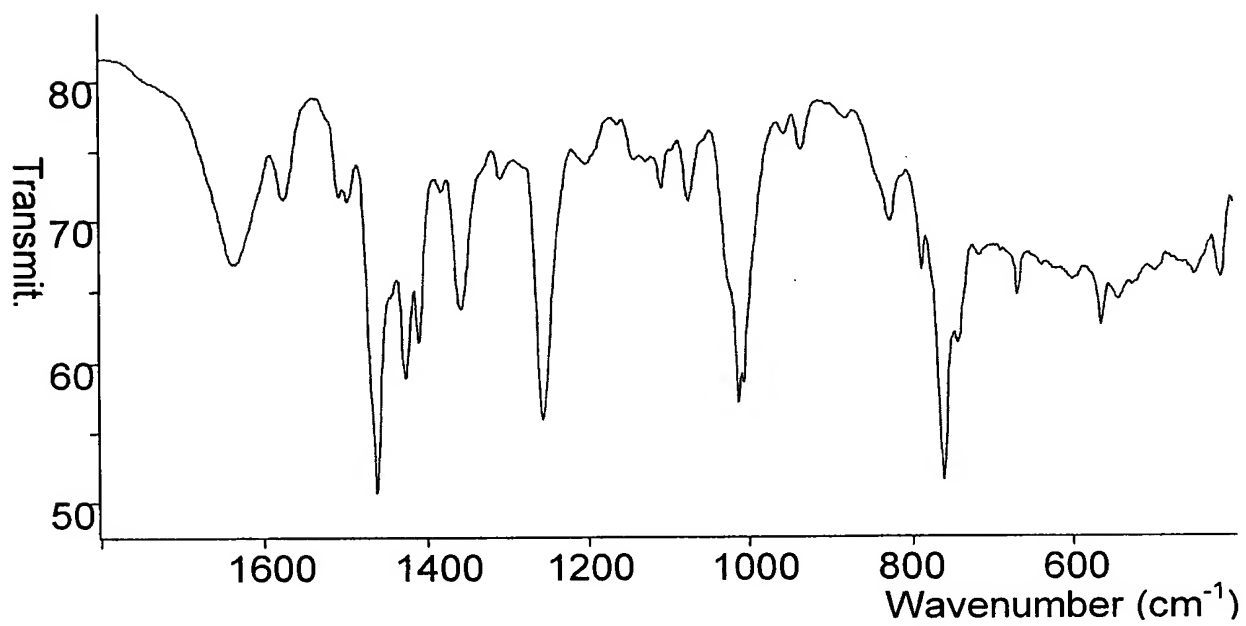


Figure 10

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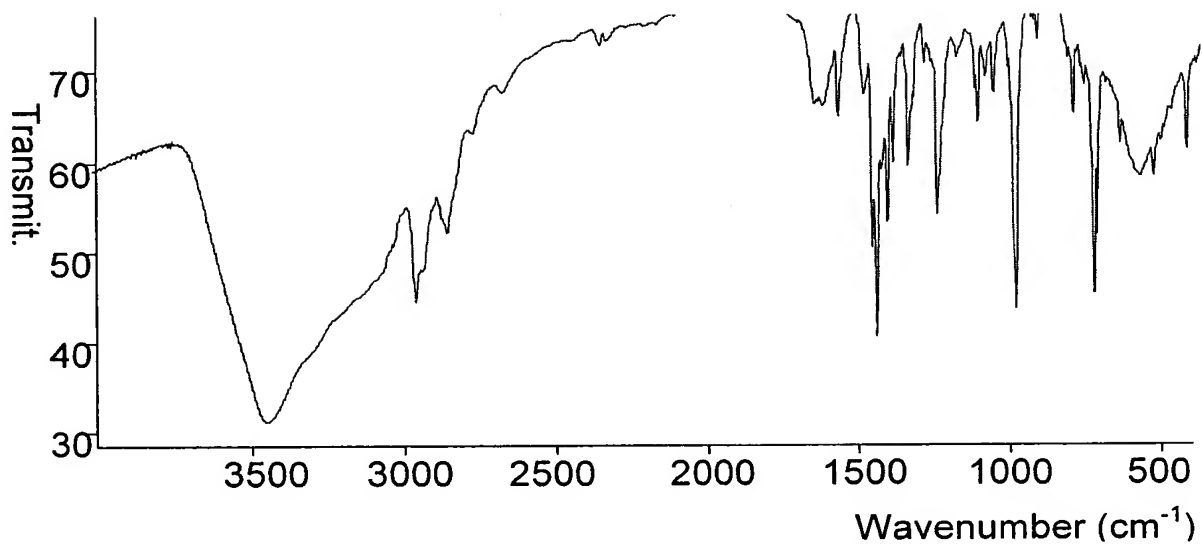


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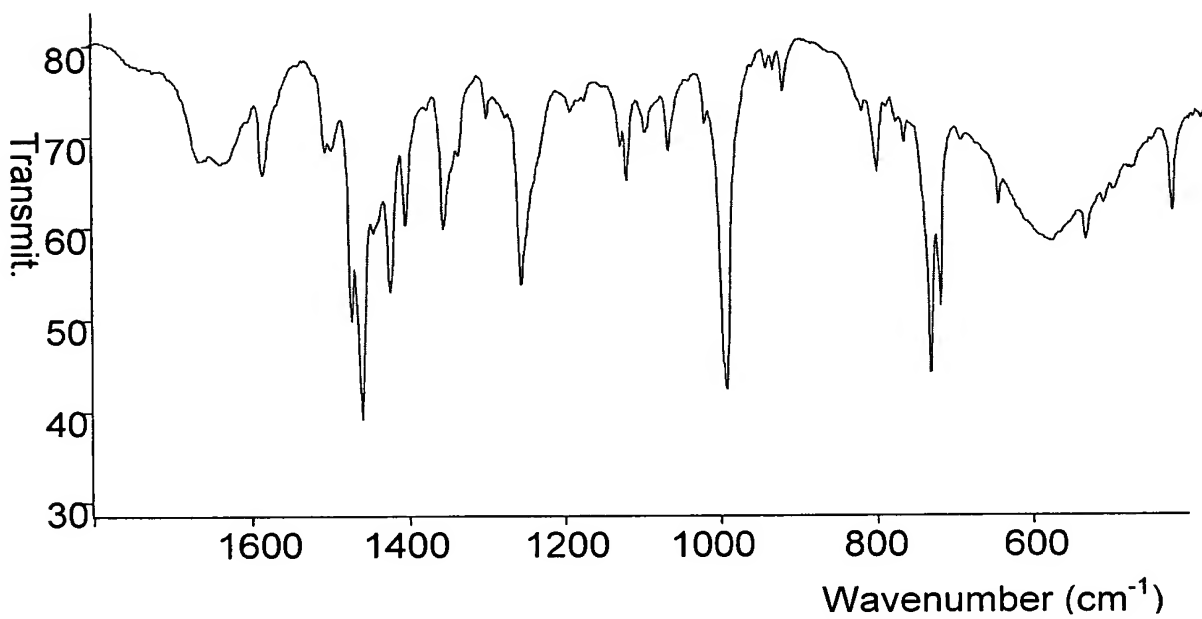


Figure 12

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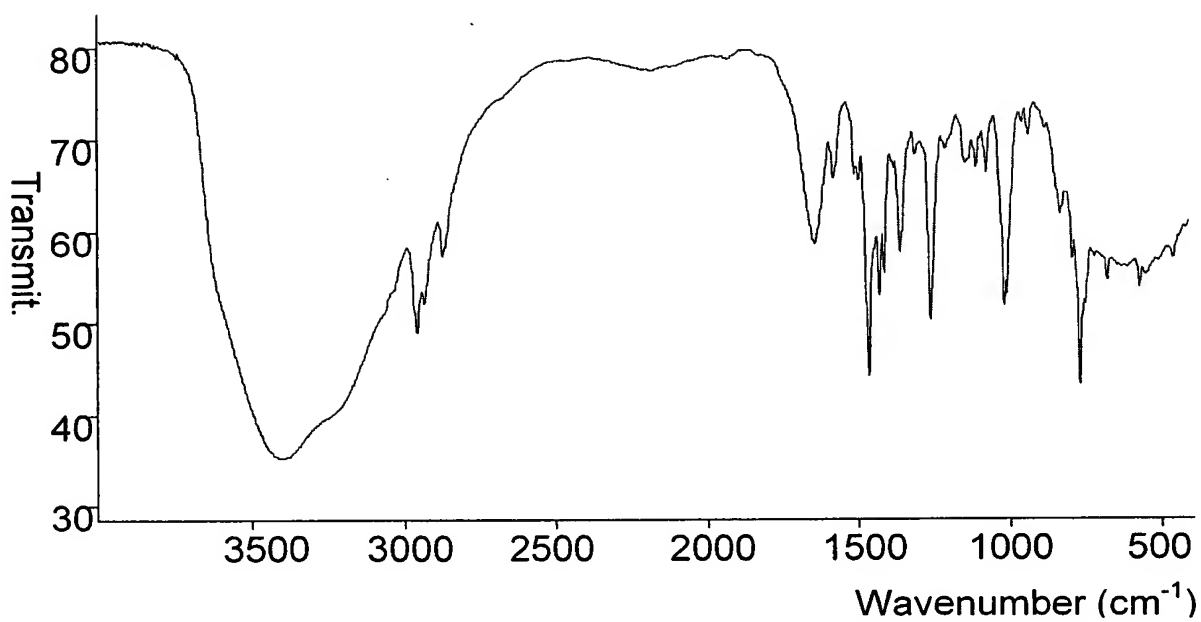


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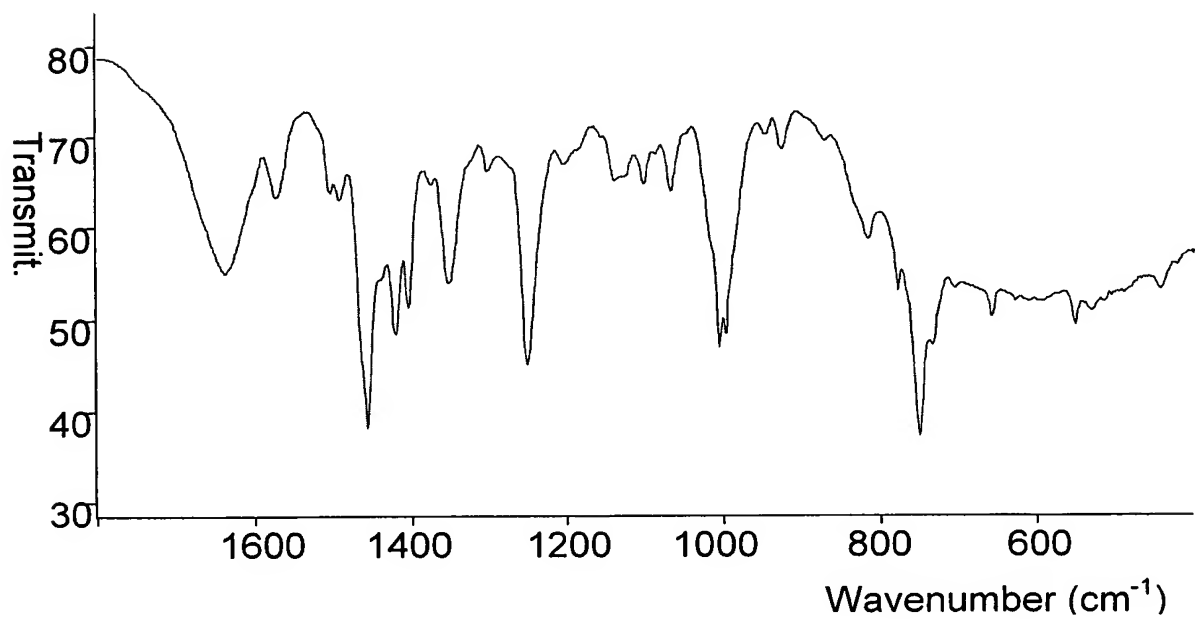


Figure 14

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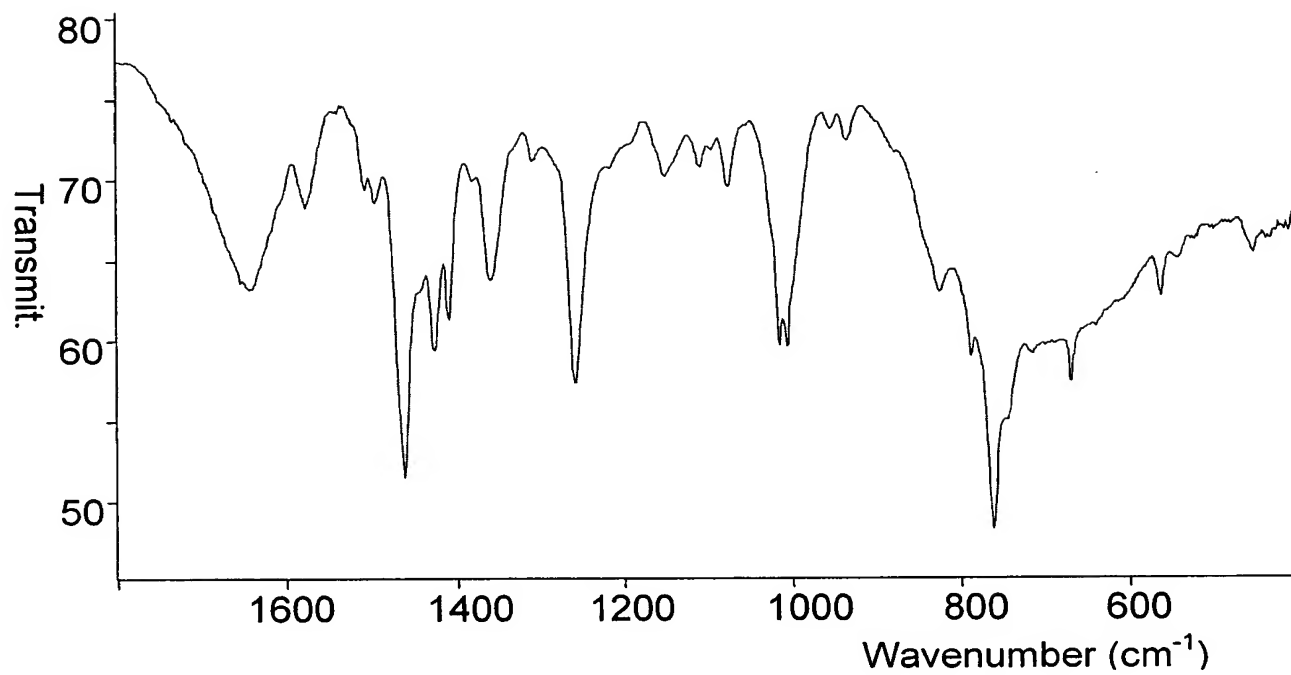


Figure 15

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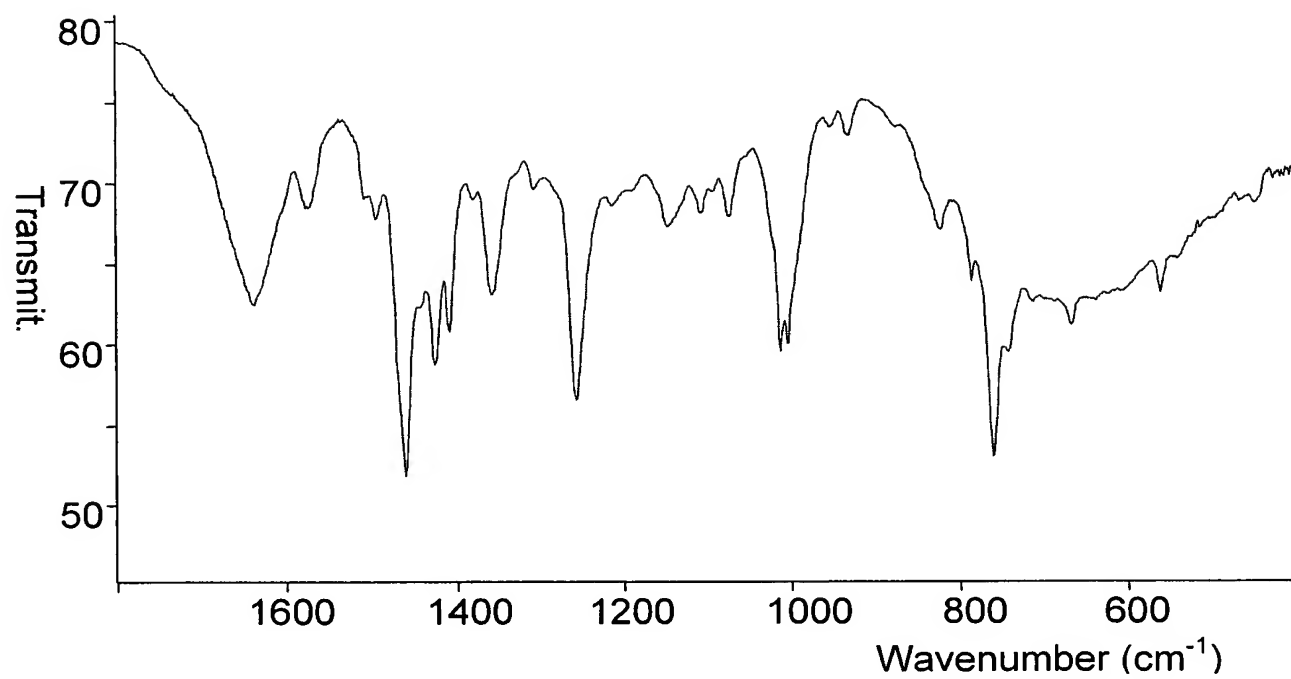


Figure 16

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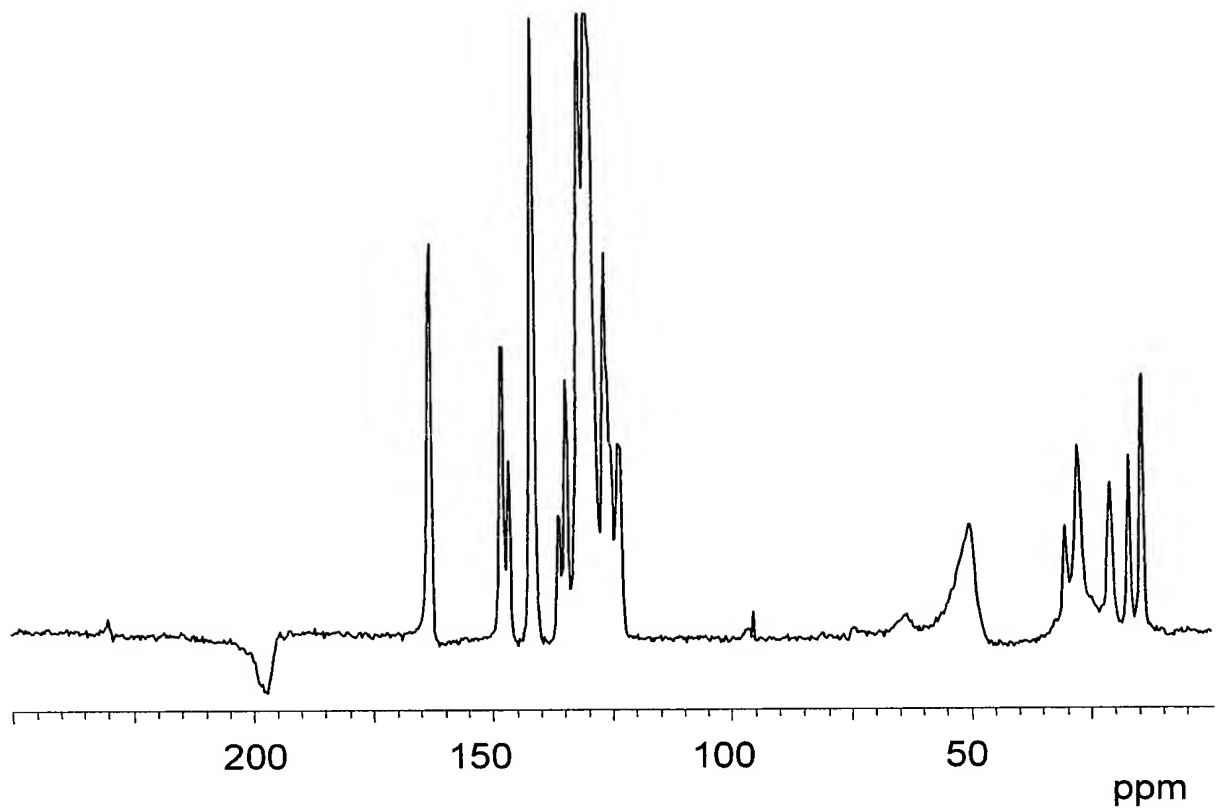


Figure 17

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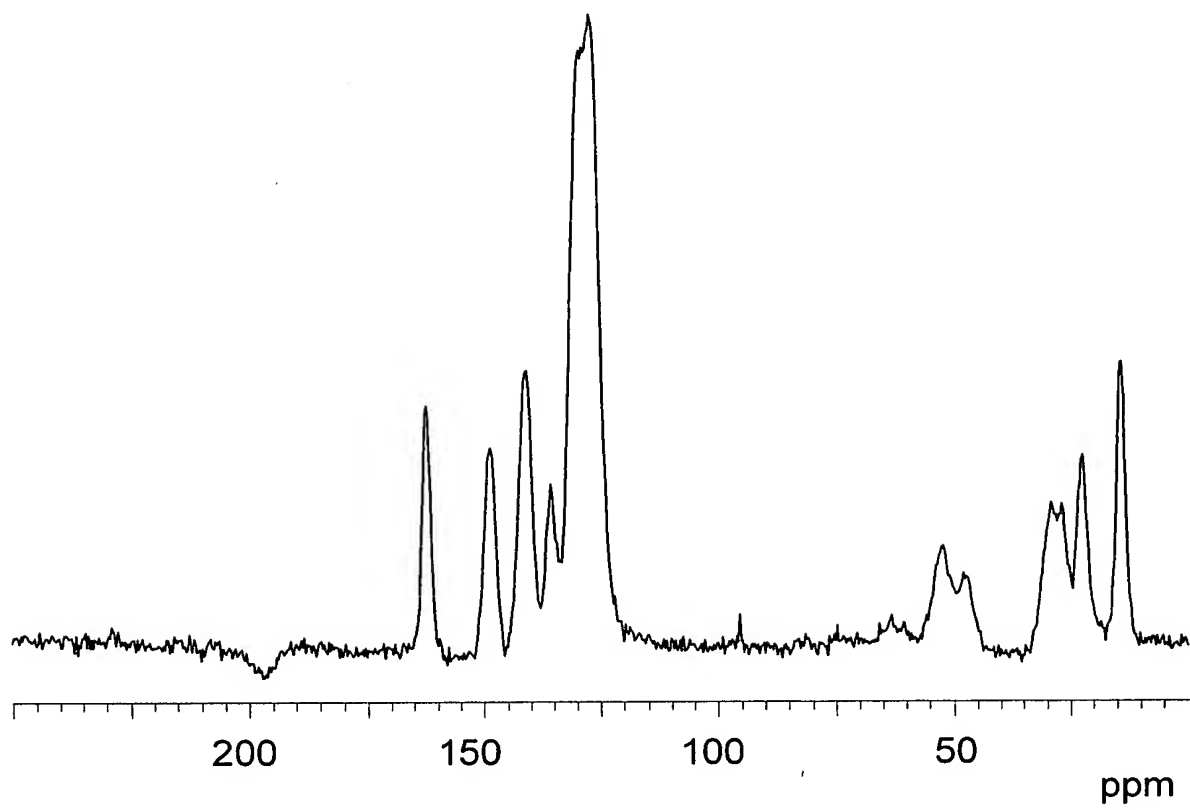


Figure 18

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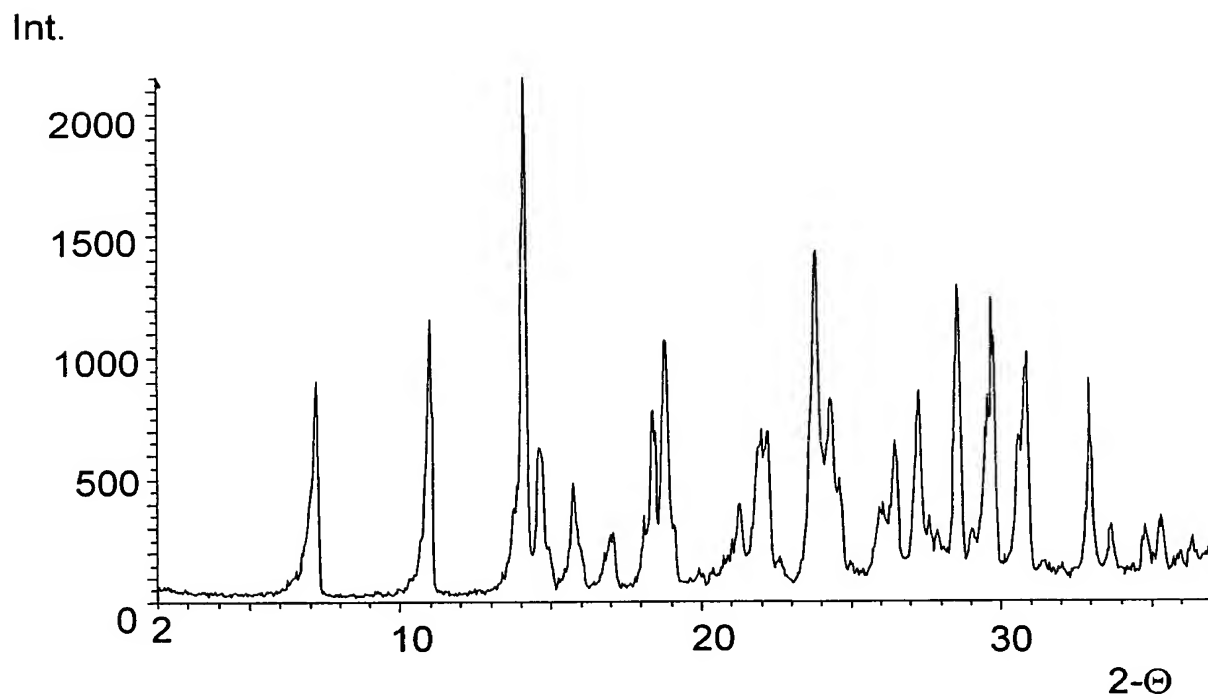


Figure 19

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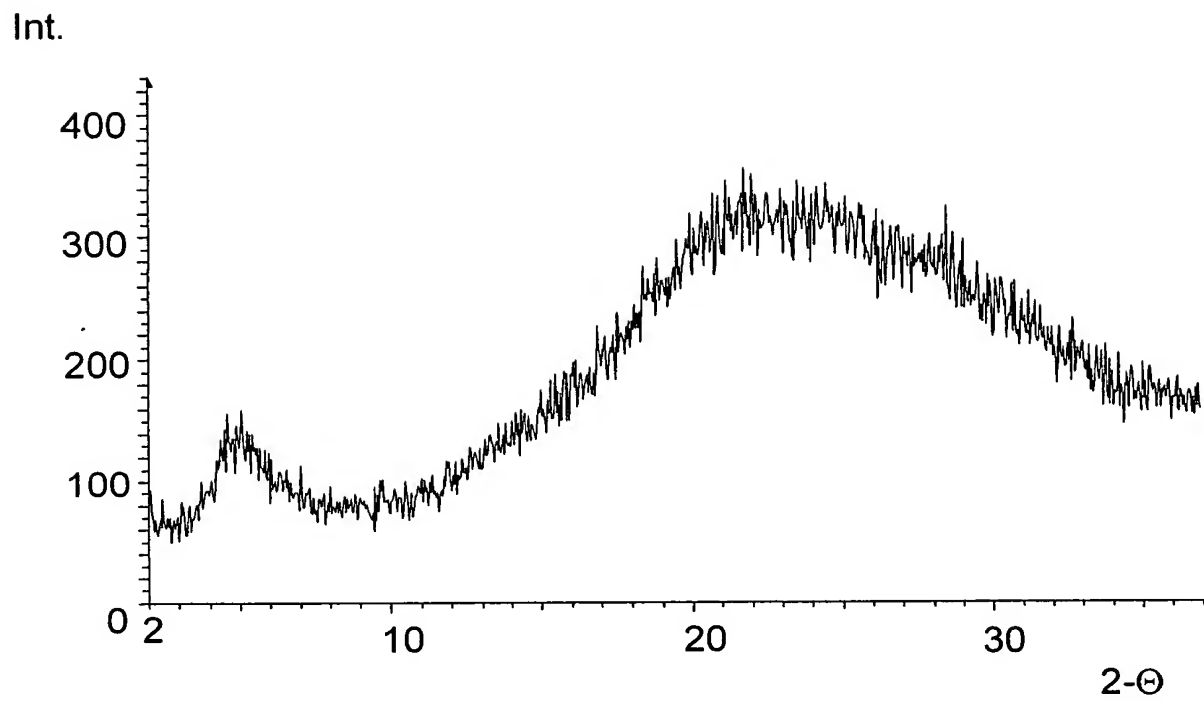


Figure 20

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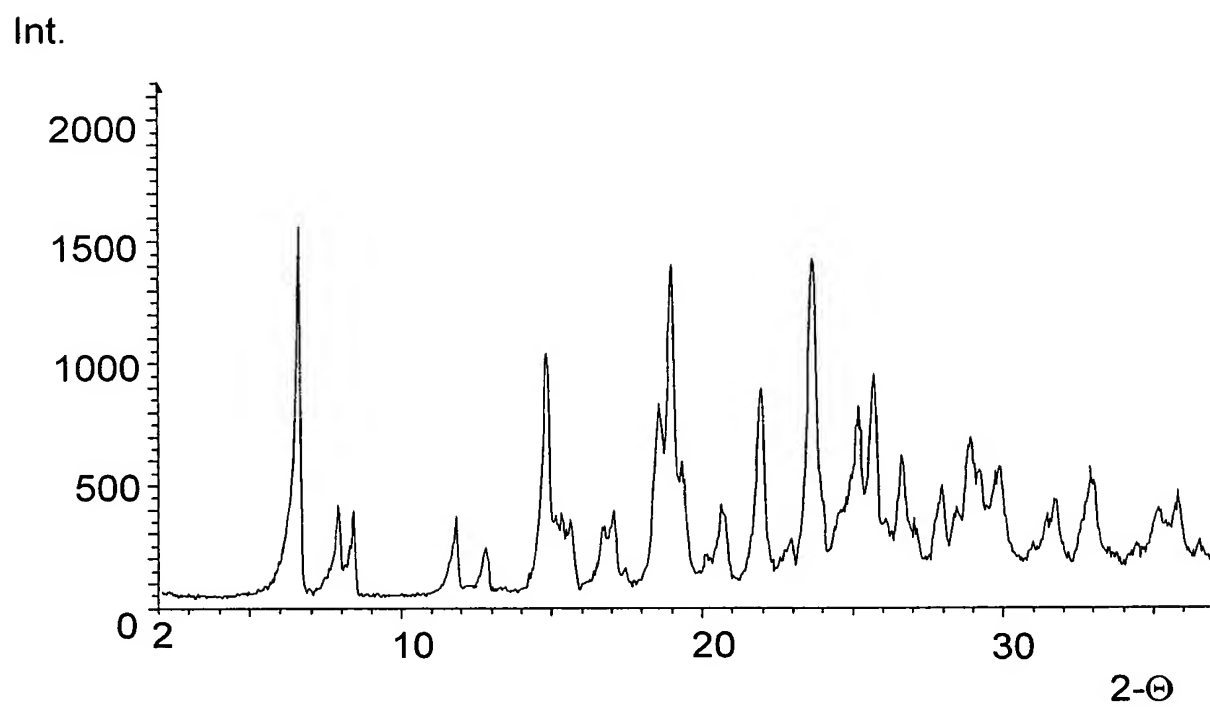


Figure 21

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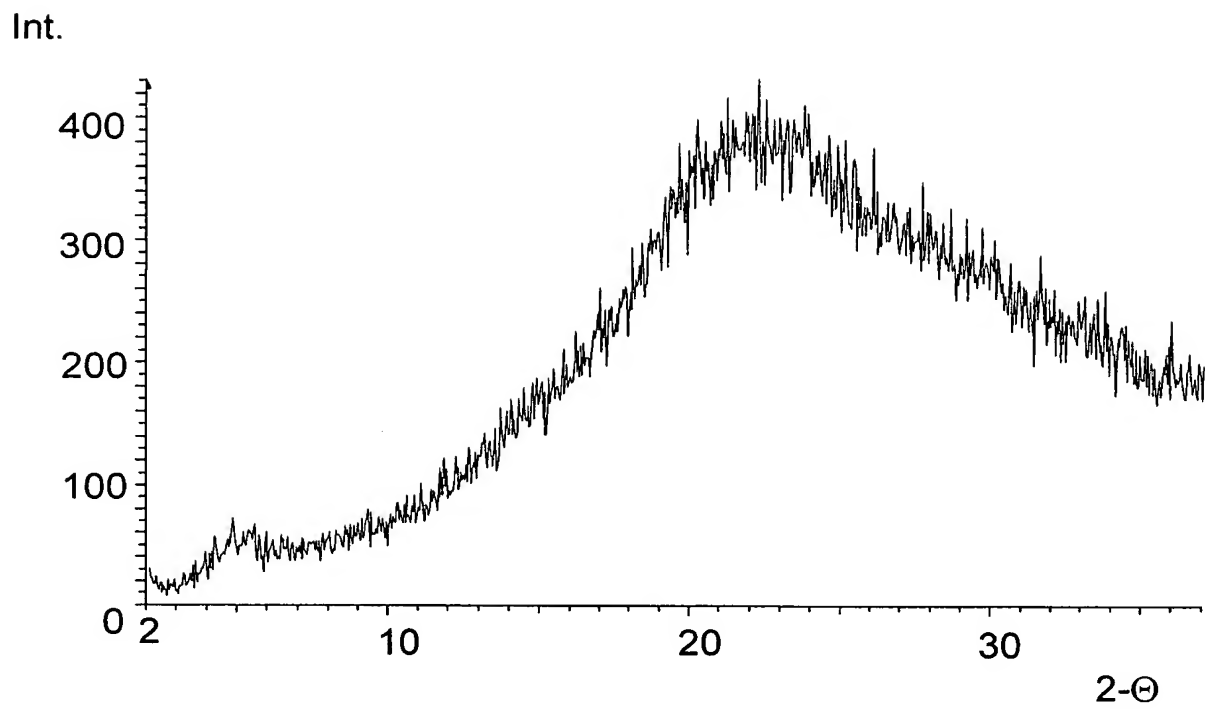


Figure 22

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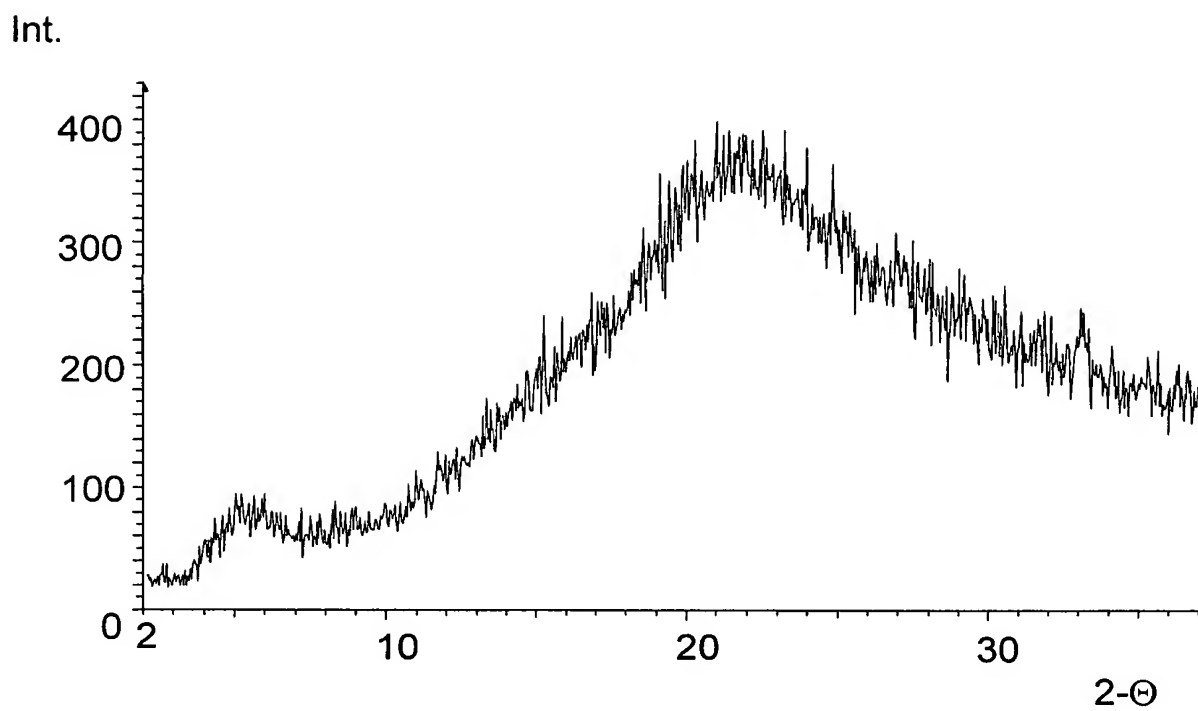


Figure 23

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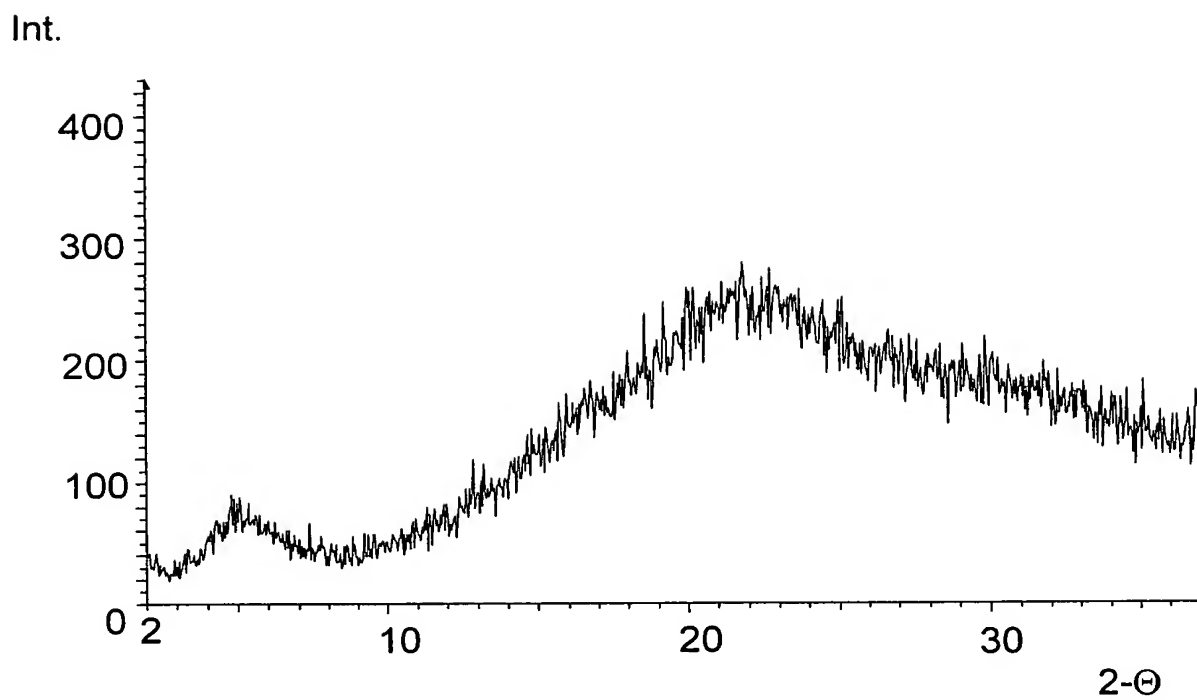


Figure 24

The undersigned Djurdjica Mandrino, permanent court interpreter for the English language, appointed by Decree No. 756-4/91, issued on 11<sup>th</sup> of February 1991 by the Ministry of Justice and Administration, Republic of Slovenia, hereby declares that this document entirely corresponds to the original Slovene text.

Ljubljana, 21 March 2005

